

# For Reference

---

NOT TO BE TAKEN FROM THIS ROOM

# For Reference

NOT TO BE TAKEN FROM THIS ROOM

Ex LIBRIS  
UNIVERSITATIS  
ALBERTAENSIS





Digitized by the Internet Archive  
in 2020 with funding from  
University of Alberta Libraries

<https://archive.org/details/Bowman1968>





THE UNIVERSITY OF ALBERTA

Synthetic Studies on Lycopodium Alkaloids

by

William Russell Bowman



A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES  
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE  
OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

February, 1968



UNIVERSITY OF ALBERTA  
FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "Synthetic Studies on Lycopodium Alkaloids" submitted by William Russell Bowman B.Sc. (Hons.) in partial fulfillment of the requirements for the degree of Doctor of Philosophy.



## ACKNOWLEDGEMENTS

The author wishes to thank:

Mr. R. N. Swindlehurst and associates for the measurement of infrared and nuclear magnetic resonance spectra and for chemical analyses; and Mr. G. Bigam and associates for the measurements of 100 Mc/s nuclear magnetic resonance spectra.

Mr. A. Budd and Mr. W. Duholke for the determination of the mass spectra.

The National Research Council and the University of Alberta for financial support.

The academic and technical staff of the Department of Chemistry, University of Alberta, for their co-operation and advice during the research project.

Mrs. Mary Waters for the typing of this manuscript.

Mr. A. C. Soper, Dr. P. Smith, and Dr. T. C. Joseph for their collaboration and help in this research project, and to Mr. J. F. McCutcheon for his technical assistance.

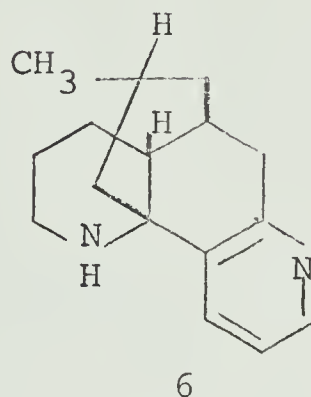
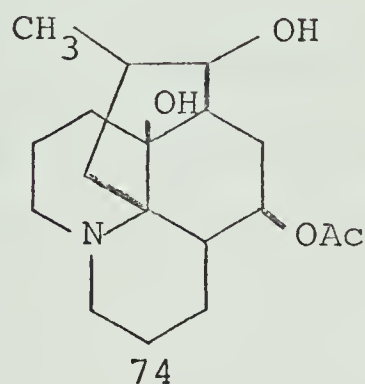
Especially to Dr. W. A. Ayer for the excellent and considerate guidance and encouragement he provided throughout the project and for the knowledge he imparted to me.

---



ABSTRACT

The structure of the Lycopodium alkaloid lycofawcine (base L) (74) isolated by R. H. Burnell has been determined by the use of mass spectral analysis. The proposed structure was confirmed by transformation of lycofawcine into O-acetylacrifoline.



The total synthesis of lycodine (6) was attempted but was not brought to a successful conclusion.

The total synthesis of dl-lycopodine (1) has been achieved via a natural relay compound. A method for transforming 11-substituted cis-cis-hexahydrojulolidines (A) into the corresponding cis-trans-hexahydrojulolidines (B) has been developed.

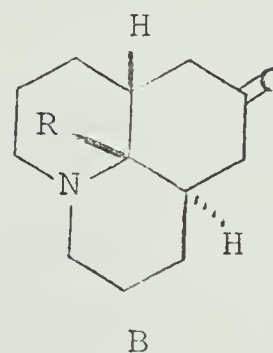
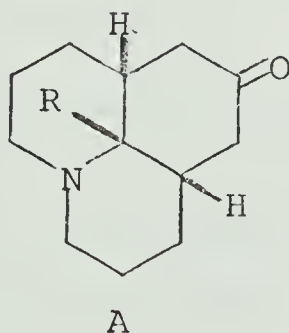
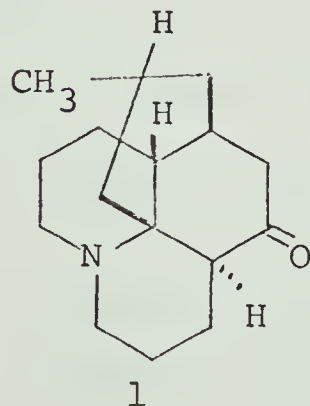






TABLE OF CONTENTS

	<u>Page</u>
INTRODUCTION . . . . .	1
Part 1: The structural elucidation of lycofawcine	
Discussion and results . . . . .	22
Experimental . . . . .	31
Mass spectra	
Figure 1. Lycofawcine . . . . .	35
Figure 2. Dehydrolycofawcine . . . . .	35
Figure 3. Desacetyllycofawcine . . . . .	35
Figure 4. Desacetyldehydrolycofawcine . . . . .	35
Figure 5. Acetyllycofawcine . . . . .	35
Infrared spectra	
Figure 6. O-Acetylacrifoline in carbon tetra- chloride . . . . .	36
Figure 7. Dehydrolycofawcine in carbon tetra- chloride . . . . .	36
Figure 8. Lycofawcine in chloroform . . . . .	36
Part 2: The Attempted synthesis of Lycodine	
Discussion and results . . . . .	37
Experimental . . . . .	55
Nuclear Magnetic Resonance Spectra	
Figure 9. The hydroxy imine 101 in deuterio- chloroform . . . . .	80
Figure 10 The imine 98 in deuteriochloroform . . . .	80
Figure 11 The amine 118 in deuteriochloroform . . . .	80



## Infrared Spectra

Figure 12. The hydroxy imine 101 in chloroform . . .	81
Figure 13. The hydroxy amine 107 or 108 in nujol . .	81
Figure 14. The N-methylamine 119 in carbon tetra chloride . . . . .	81

## Part 3: The synthesis of lycopodine

Discussion and results. . . . .	82
Experimental . . . . .	117

## Mass spectra

Figure 15. The methoxy ketone 164 . . . . .	163
Figure 16. The methoxy ketones 167 and 168 . . . .	163
Figure 17. The lactams 177 and 184 . . . . .	163

## Nuclear Magnetic Resonance Spectra

Figure 18. The hydroxy ketone 142 in deuterio chloroform . . . . .	164
Figure 19. The acetoxy $\alpha,\beta$ -unsaturated 2,4- dinitrophenylhydrazone in deuterio- chloroform . . . . .	164
Figure 20. The ether 160 in carbon tetrachloride .	164
Figure 21. The methoxy $\alpha,\beta$ -unsaturated ketone 166 reaction mixture in carbon tet- rachloride . . . . .	165
Figure 22. The methoxy lactams 178 and 179 in deuteriochloroform . . . . .	165
Figure 23. The alcohol 169 in deuteriochloroform .	165
Figure 24. The alcohol 170 in deuteriochloroform .	166
Figure 25. The lactam alcohol 181 in deuterio- chloroform . . . . .	166
Figure 26. The lactam alcohols 180 and 181 in deuteriochloroform . . . . .	166



Infrared spectra

Figure 27. The hydroxy ketone 142 in carbon tetra- rachloride . . . . .	167
Figure 28. The ether 160 in carbon tetrachloride. . .	167
Figure 29. The quaternary salt 174 in nujol . . . . .	167
Figure 30. The acetoxy $\alpha,\beta$ -unsaturated 2,4-dinitro- phenylhydrazone 154 in carbon tetra- chloride . . . . .	168
Figure 31. The acetoxy $\alpha,\beta$ -unsaturated ketone 159 in carbon tetrachloride. . . . .	168
Figure 32. The methoxy $\alpha,\beta$ -unsaturated ketone 166 reaction mixture in carbon tetrachloride .	168
Figure 33. The methoxy ketone 164 in carbon tetra- rachloride . . . . .	169
Figure 34. The methoxy ketones 167 and 168 in carbon tetrachloride . . . . .	169
Figure 35. The alcohol 170 in chloroform . . . . .	169
Figure 36. The alcohol 169 in carbon tetrachloride. .	170
Figure 37. The acetate 171 in carbon tetrachloride. .	170
Figure 38. The acetate 172 in carbon tetrachloride. .	170
Figure 39. The methoxy lactams 178 and 179 in carbon tetrachloride . . . . .	171
Figure 40. The lactam alcohols 180 and 181 in chloroform . . . . .	171
Figure 41. The mesyl lactams 185 and 186 in chloroform . . . . .	171
Figure 42. The lactam acetate 188 in carbon tetrachloride. . . . .	172
Figure 43. The lactam alcohol 181 in chloroform . . .	172
Figure 44. The lactam alcohol 180 in chloroform . . .	172



Figure 45. The lactams 177 and 184 in chloroform . . .	.173
Figure 46. The lactam 184 in chloroform . . . . .	.173
Figure 47. The lactam 177 in chloroform . . . . .	.173
Bibliography . . . . .	.174

---

---

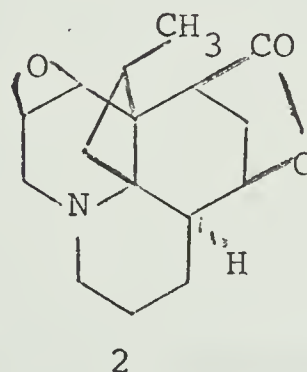
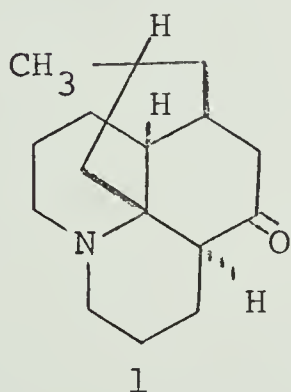




## INTRODUCTION

In recent years numerous publications dealing with the structural elucidation of alkaloids in the Lycopodiaceae have appeared. The number of new structures of Lycopodium alkaloids has increased considerably in the last few years until at present some thirty are known. Several publications concerning interconversions between various alkaloids of this group have also appeared but until very recently none had yielded to synthesis.

Lycopodine (1), the major alkaloid present in most of the Lycopodium species, was the first to be isolated. Although lycopodine was isolated in 1881,<sup>1</sup> its structure was only determined in 1960.<sup>2a-e</sup>

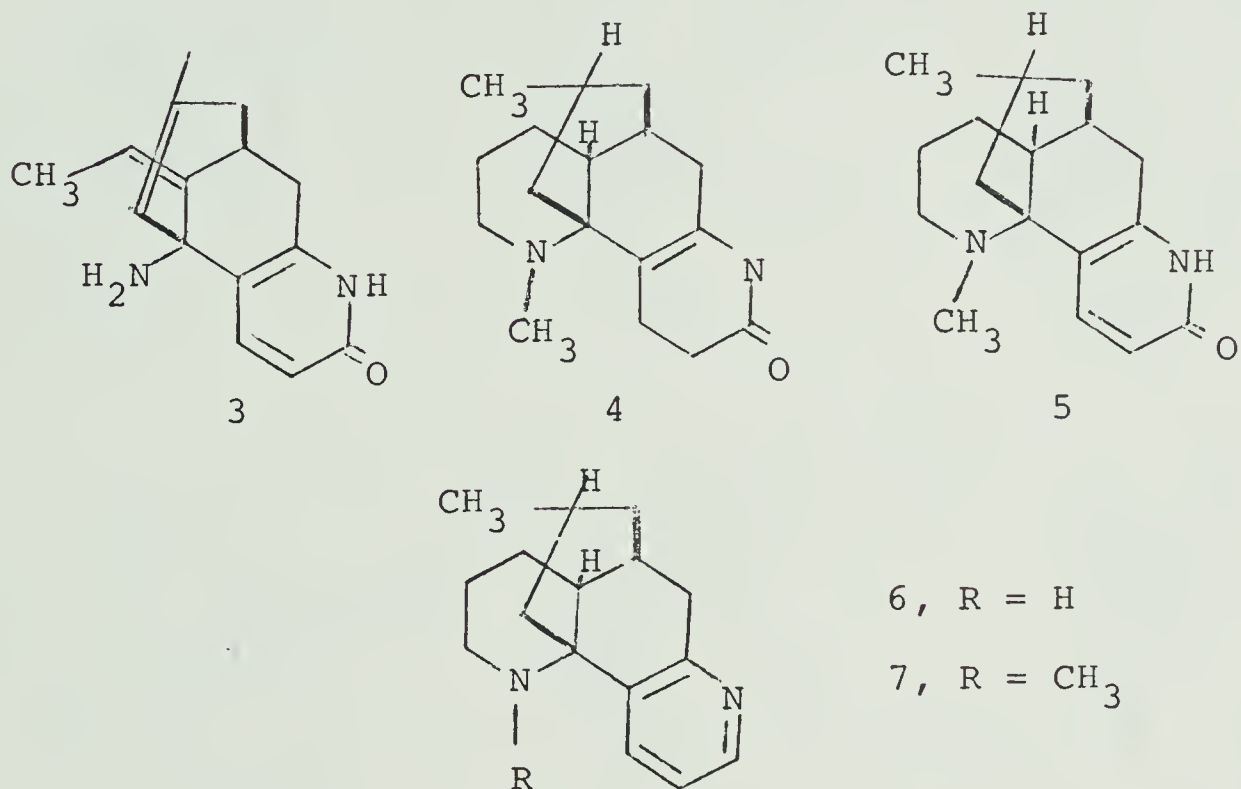


Annotinine (2) was the first Lycopodium alkaloid, the structure of which was completely elucidated.<sup>3</sup> Annotinine remains unique, being the only Lycopodium alkaloid to contain a cyclobutane ring.

Following the determination of the structure of lycopodine in 1960, the structures of several alkaloids with



the same ring skeleton were elucidated. During this period a new group of Lycopodium alkaloids containing two nitrogen atoms was found. This group consists of selagine (3)<sup>4</sup>,  $\alpha$ -obscurine (4)<sup>5</sup>,  $\beta$ -obscurine (5)<sup>5</sup>, lycodine (6)<sup>6</sup>, N-methyl-lycodine (7)<sup>5,6</sup>, and several more compounds.



In the past seven years Lycopodium alkaloids of widely differing structures have been isolated and their structures elucidated. These alkaloids can be classified into several groups which are represented as follows.

- 1). Lycopodine. This is the fundamental group and the only one which contains a large variety of compounds with different substituents.

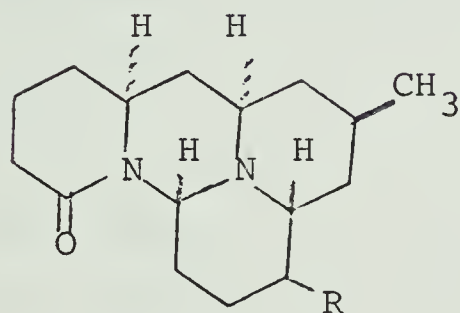
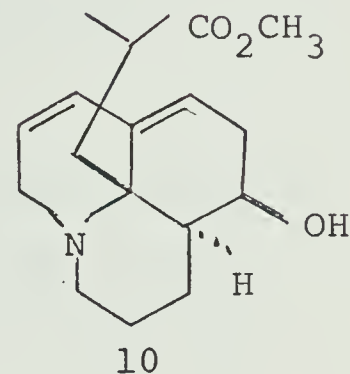
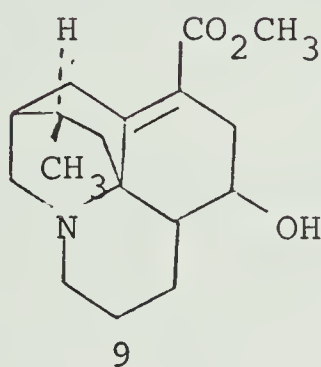
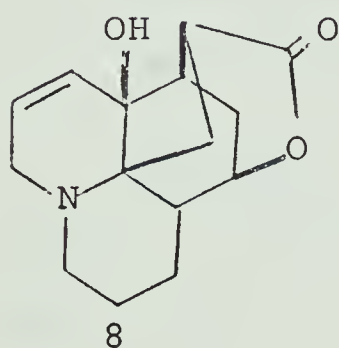


2). Annotinine.

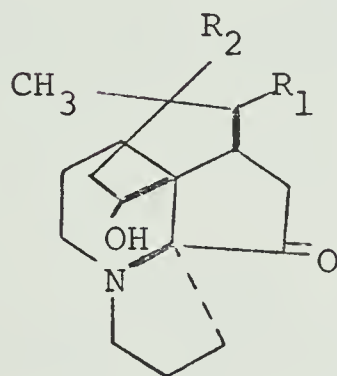
3). Selagine.

4).  $\alpha$ -Obscurine. This group includes  $\beta$ -obscurine and lycodine.

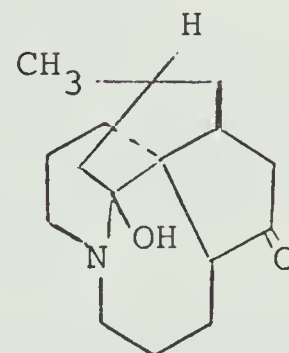
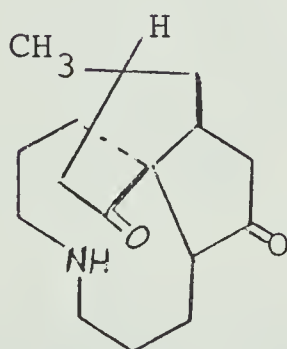
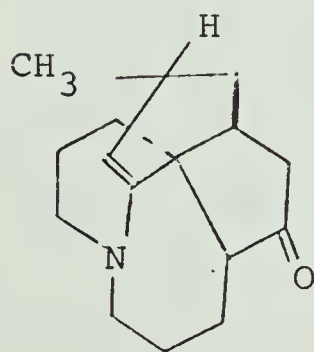
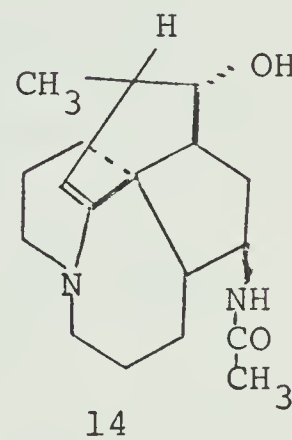
5.) Annotine (8).<sup>7</sup>



12, R = OH



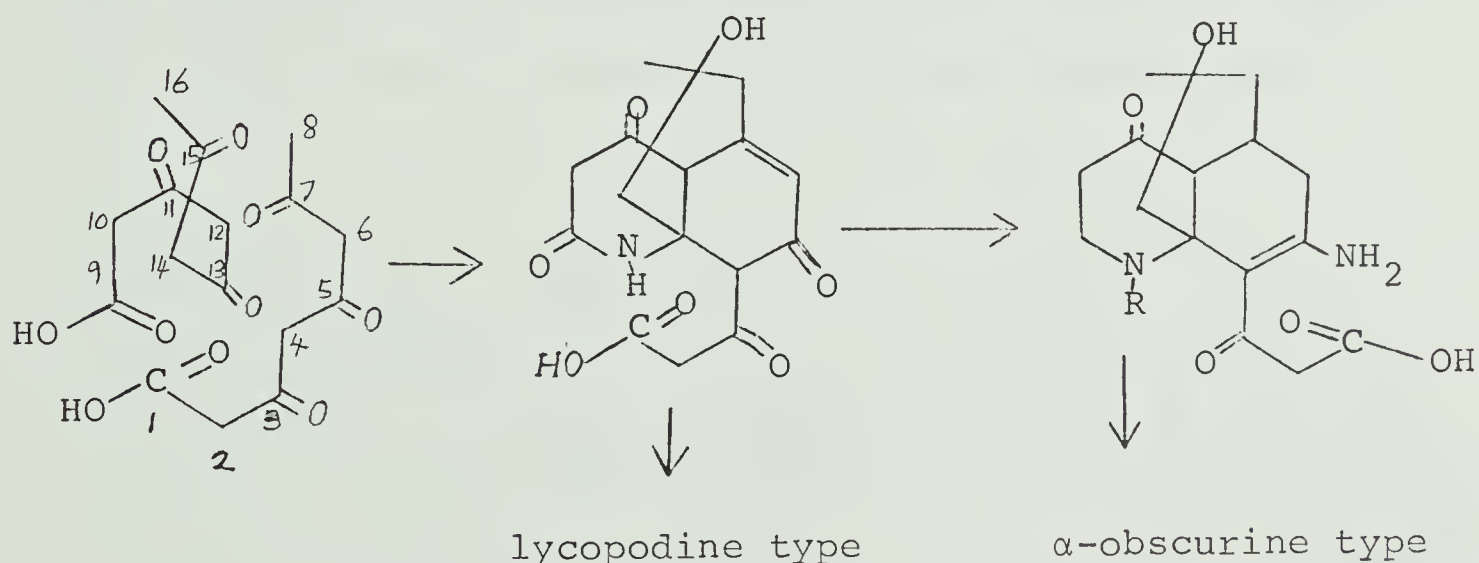
17, R<sub>1</sub> = H, R<sub>2</sub> = OH





- 6). Annopodine (9).<sup>8</sup>
- 7). Lyconnotine (10).<sup>9</sup>
- 8). Cernuine (11).<sup>10,11,12</sup> This group also includes lycocernuine (12).
- 9). Serratinine (13).<sup>13</sup> This group includes serratini-  
dine (14).<sup>14</sup> fawcettidine (15),<sup>15</sup> fawcettimine (16).<sup>16</sup>  
and serratine (17).<sup>17</sup>

Although these various groups are different structurally, a consideration of their biogenesis shows their similarity. No experimental results in this field have been published; however Conroy<sup>18</sup> has suggested that the Lycopodium alkaloids may be biosynthesised through condensation of two 3,5,7-triketooctanoic acid units with one or two equivalents of ammonia. These assumptions have been useful as an aid to structural elucidation and also have supplied the numbering system for the group.



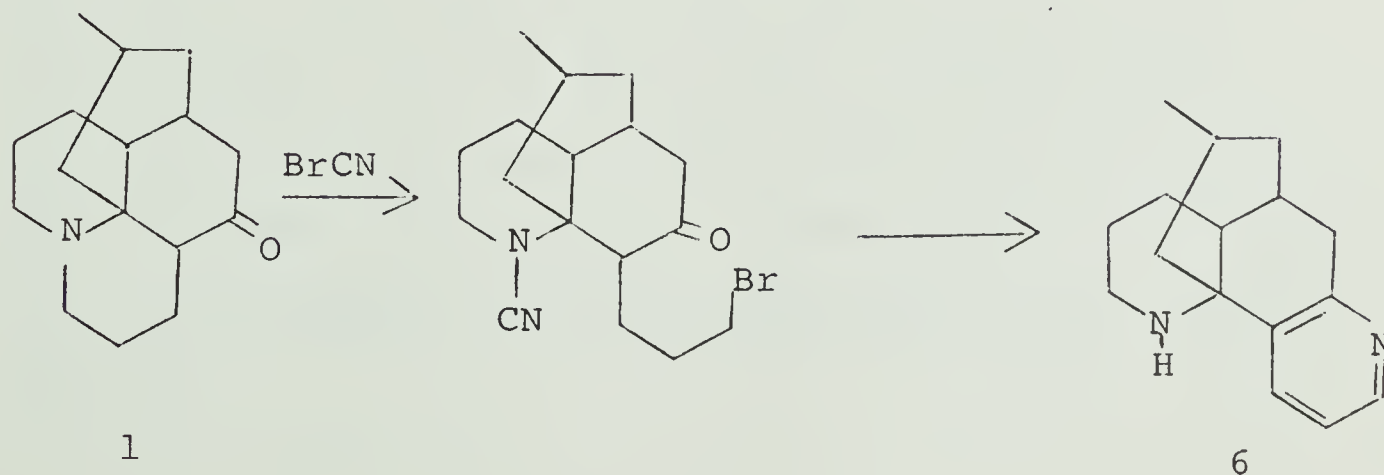




Cernuine represents a third type of condensation. Lycopodine has been described <sup>19</sup> as a possible central alkaloid from which the other alkaloids are obtained by oxidation and/or rearrangement as indicated by its relatively larger occurrence. Lycopodine is thus of prime importance among the Lycopodium alkaloids. This has therefore led to considerable interest in its conversion into other Lycopodium alkaloids and to its total synthesis.

The earlier synthetic studies in Lycopodium chemistry dealt only with transformations between various alkaloids. These studies were used for the purpose of correlating proposed structures with those already known, particularly in determining stereochemistry. The methods and the intermediates also now serve the purpose of relay compounds for total synthesis.

The structure of lycodine (6) was thus confirmed by Anet and Rao <sup>20</sup> who converted lycopodine (1) into lycodine (6). This sequence along with the total synthesis of



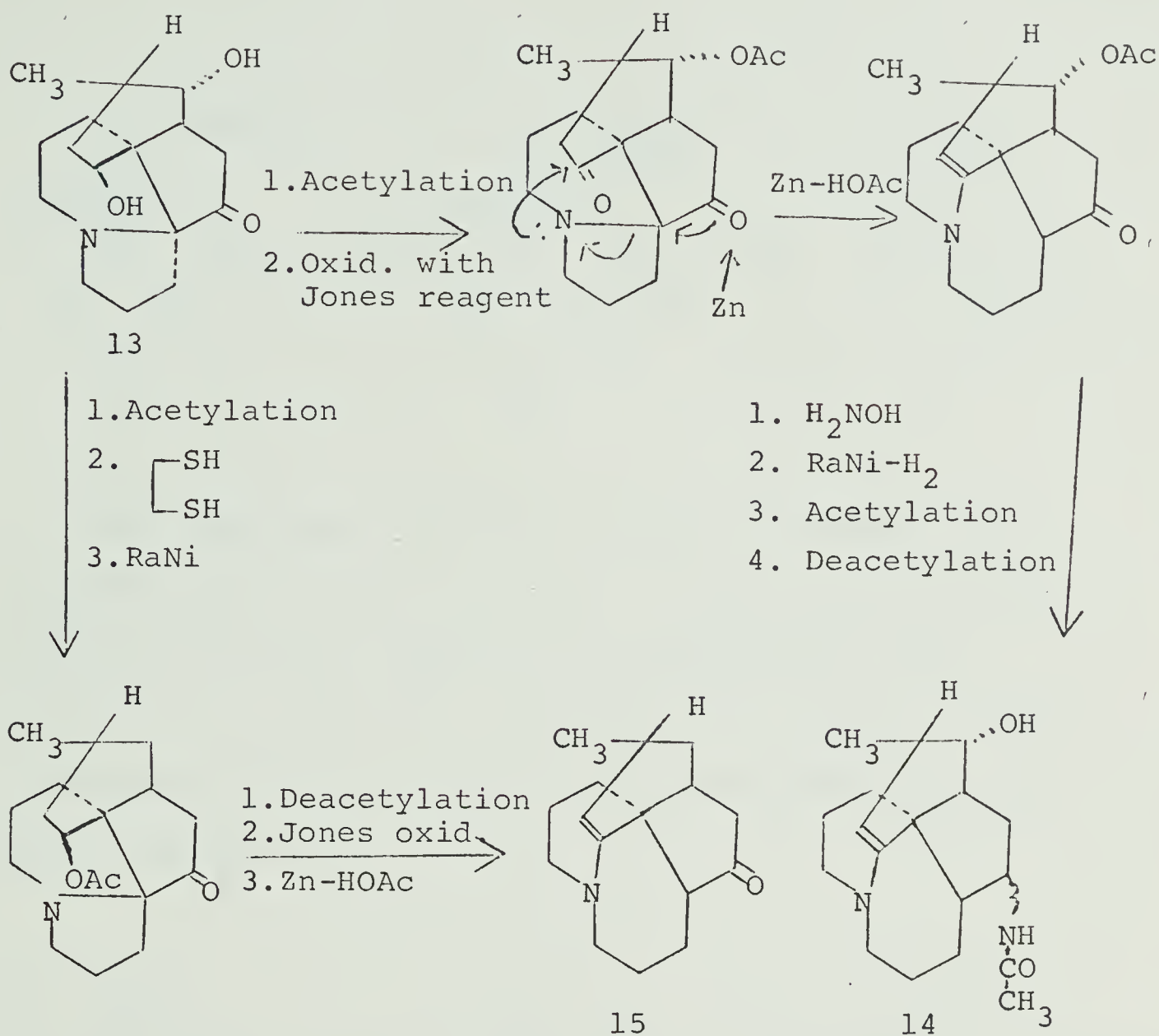


lycopodine would therefore represent in a formal sense the synthesis of lycodine. Ayer and co-workers <sup>6</sup> have converted  $\beta$ -obscurine into  $\alpha$ -obscurine and into lycodine. As a further confirmation,  $\alpha$ -obscurine has been converted <sup>5</sup> into dihydrolycopodine via lycopodine lactam.

A considerable number of interconversions within the lycopodine group have been reported. Publications have appeared on the conversion <sup>2b</sup> of lycopodine and annofoline to anhydrodihydrolycopodine. Burnell and Taylor have converted fawcettiine <sup>21</sup> to annofoline, as well as lycofoline <sup>22</sup> into acrifoline via the so-called base M. Acrifoline had previously been converted into annofoline by French and Maclean <sup>23</sup>. Ayer and co-workers have also converted lycopodine to alkaloid L.20 <sup>2f</sup>, and L.20 to lycoclavine. <sup>24</sup> More recently Ayer, Law, and Piers <sup>25</sup> have synthesised annofoline from lycopodine. This sequence involves inverting the stereochemistry at C<sub>15</sub>.

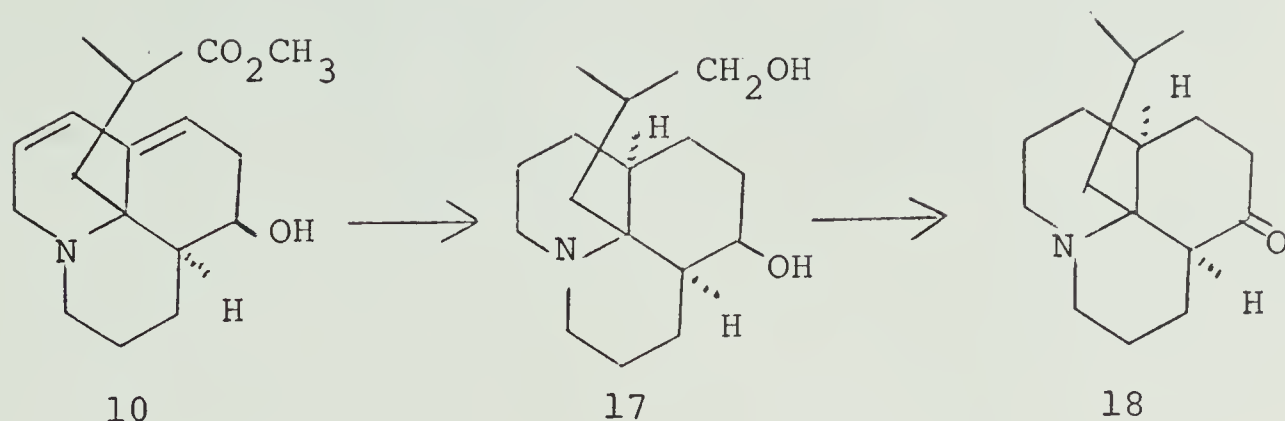
Several correlations in the serratinine group have been made. Serratinine (13) was first converted into serratinidine (14) <sup>14</sup> as shown below. Serratinine was also converted into fawcettidine (15) <sup>15</sup> using a similar zinc in acetic acid reduction. Fawcettimine (16) <sup>16</sup> which is a carbinolamine, has been dehydrated to yield fawcettidine (15).



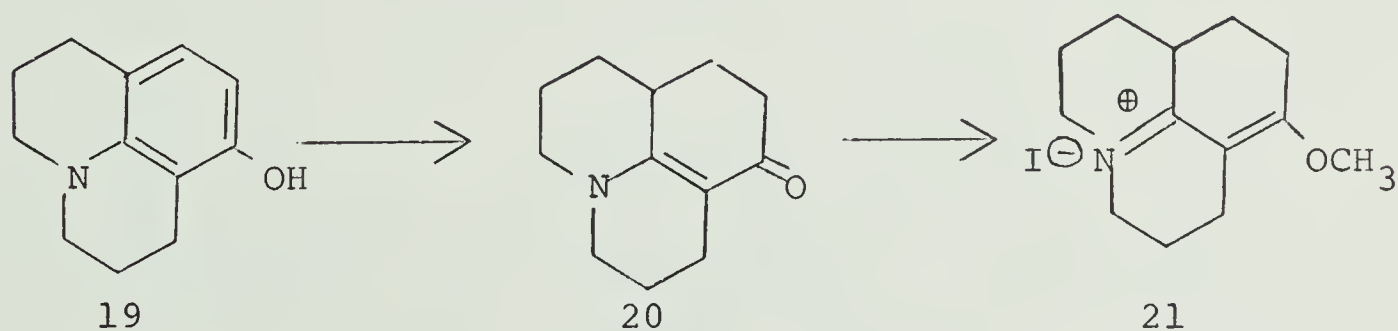


The first publication dealing with synthetic work from readily available simple chemicals was the proof of the structure of lyconnotine (10) by Wiesner, Valenta and co-workers. Lyconnotine was reduced with lithium aluminum hydride to an alcohol, which was hydrogenated with platinum in ethanol to yield the diol 17. The diol 17 was converted by a series of reactions to the ketone 18 which was then synthesised.





The synthesis of ketone 18 involved Raney nickel catalysed reduction of the phenol 19 to form the  $\alpha,\beta$ -unsaturated ketone 20, which on treatment with methyl iodide gave the salt 21. Treatment of 21 with an excess of isobutyllithium followed by acid hydrolysis gave the racemic ketone 18.

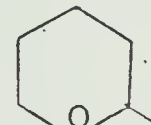
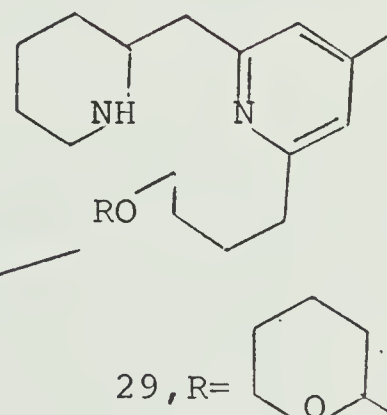
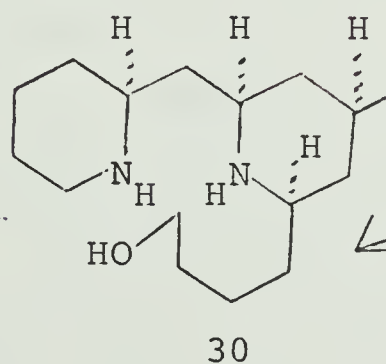
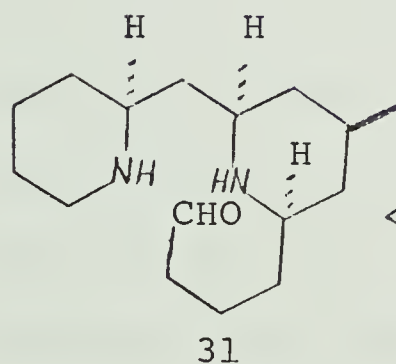
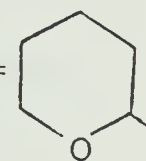
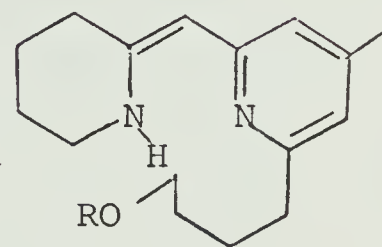
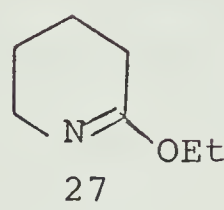
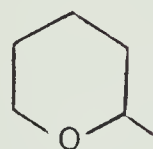
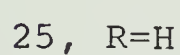
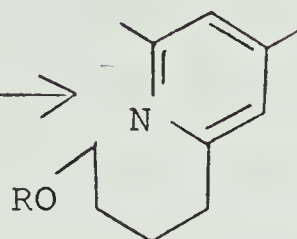
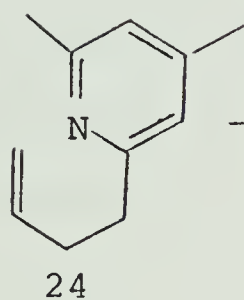
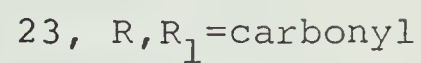
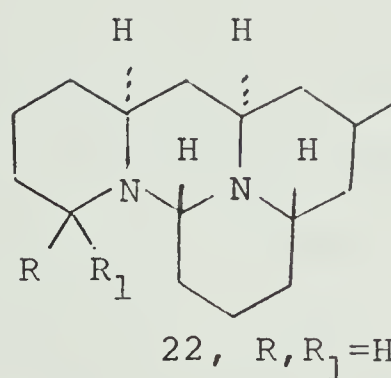
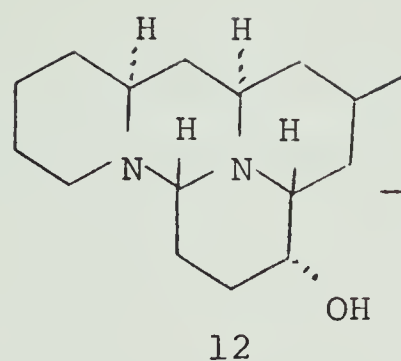


In 1966 Ayer and Piers<sup>12</sup> synthesised racemic dihydro-deoxyepiallocernuine (22) which had previously been prepared from lycocernuine (12)<sup>10,11</sup> by way of epiallocernuine (23).

This synthesis provided proof for the constitution of cernuine and lycocernuine as well as support for the stereochemical assignments.







The monolithium derivative of 2,4,6-collidine was treated with allyl bromide to give 24. After oxidative hydroboration of 24, the alcohol 25 was protected in the

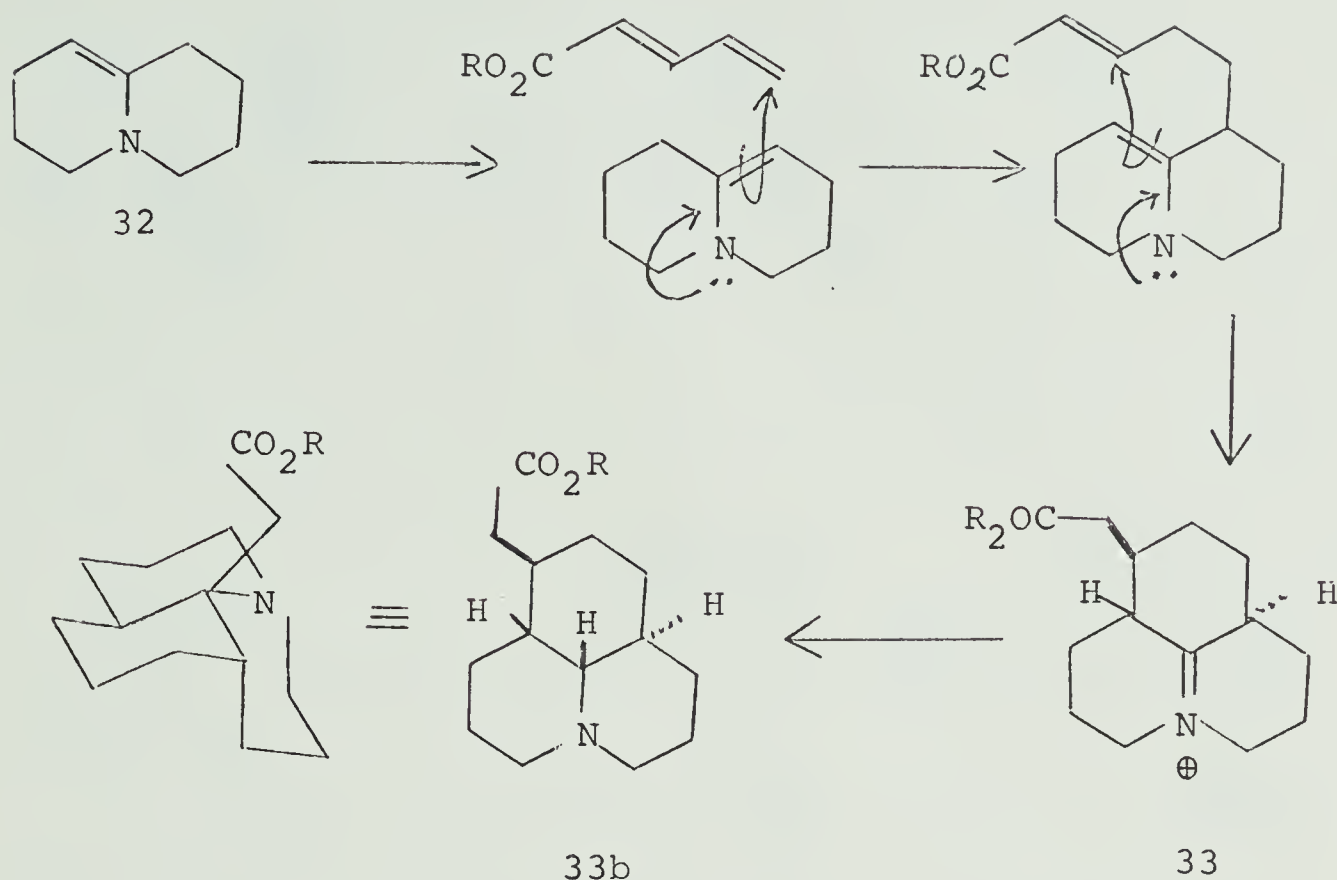


form of its pyranosyl ether 26. Condensation of 27 with the monolithium derivative of 26 gave 28, which was immediately subjected to catalytic hydrogenation to give 29. The alcohol 30 was obtained by hydrolysis of the acetal and catalytic hydrogenation at high pressure with rhodium on charcoal, and separation of the isomers by way of their N-formyl derivatives. Oxidation of 30 with chromium trioxide-pyridine gave the aldehyde 31 which spontaneously closed to dihydrodeoxyepiallocernuine (22).

Several publications have now appeared dealing with attempts at the synthesis of lycopodine. Early reports on the synthesis were by Bohlmann and co-workers. One paper <sup>27</sup> deals with the synthesis of lupinine through the use of cyclic enamines and furthering of these methods to form a stereospecific hexahydrojulolidine derivative with the lycopodine configuration. The sequence involves the use of dehydroquinolizidine (32) as an enamine for addition of the third ring to form the immonium salt 33. The stereochemistry of the immonium salt was shown by sodium borohydride reduction to the hexahydrojulolidine 33b.

Later research by Bohlmann and co-workers <sup>28</sup> involved the use of sodium borohydride in the reduction of substituted pyridine rings which could be used as

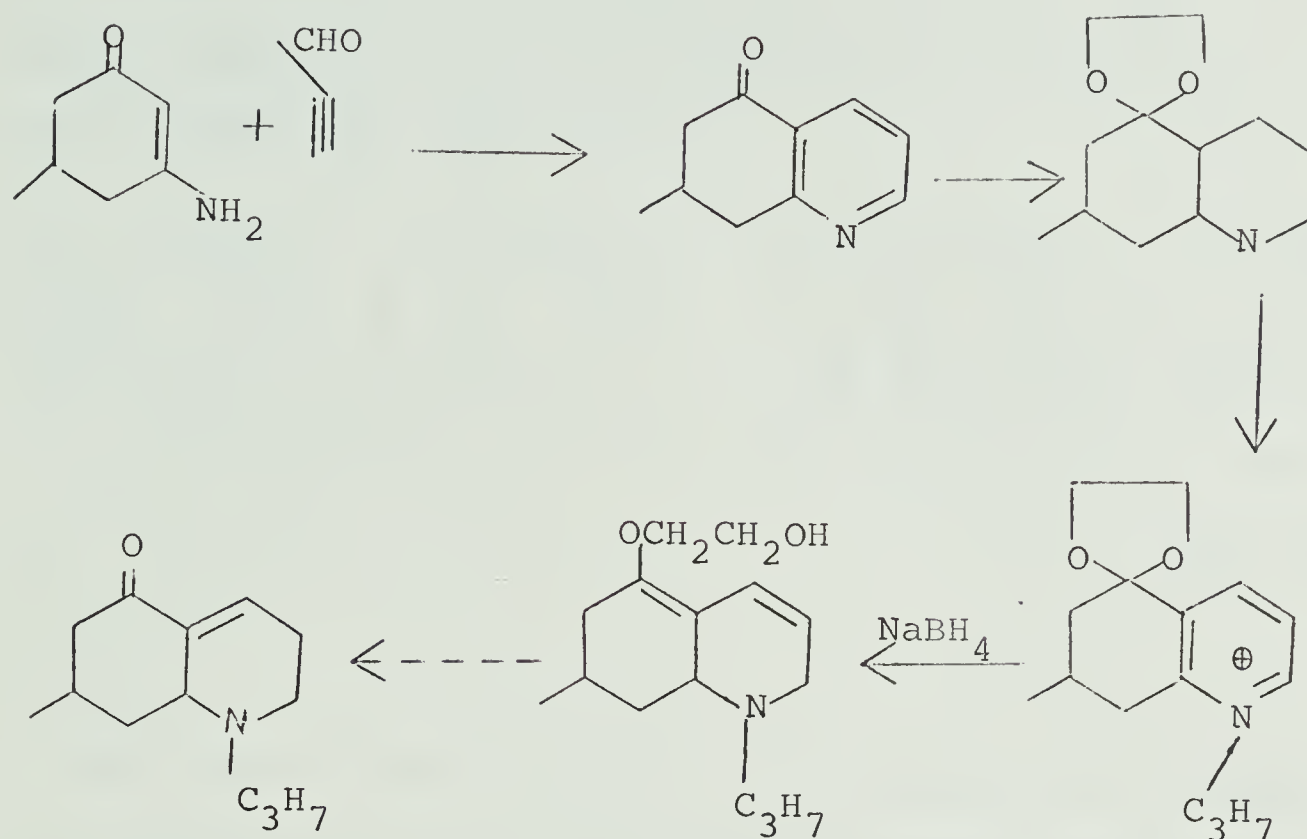




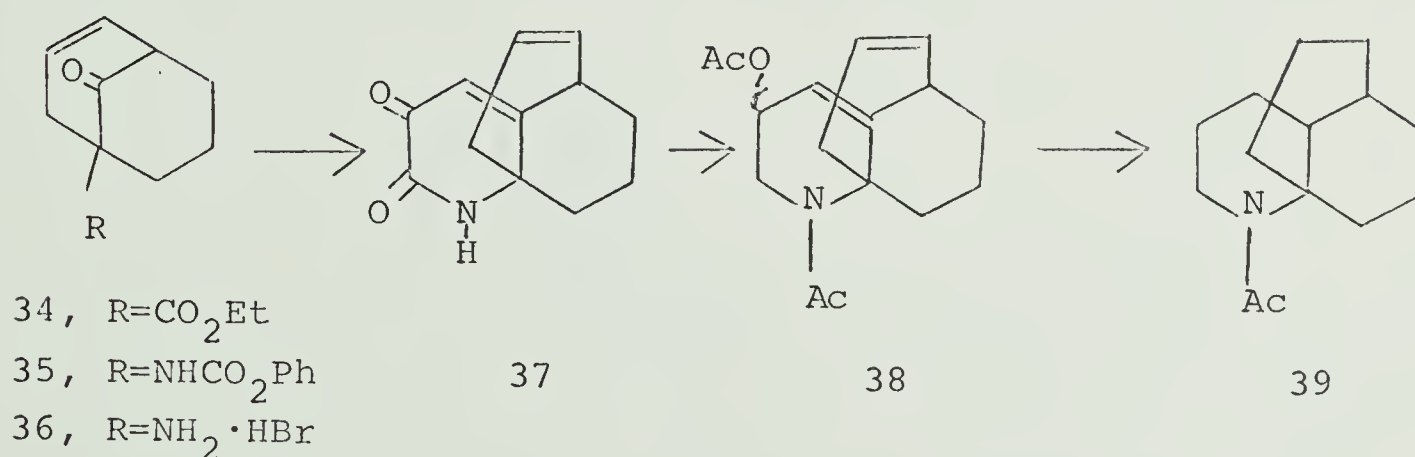
intermediates in the synthesis of lycopodine. An example of this reduction is illustrated on the next page. Further attempts <sup>29</sup> to convert the immonium salt 33 to lycopodine were unsuccessful.

Raphael and co-workers <sup>30</sup> have also endeavoured to construct a system which can be elaborated to yield lycopodine. The bicyclononane 34 was converted via the acid azide and isocyanate into the benzylcarbamate 35, which was cleaved with acid to give the amine 36. The pyruvamide of 36 gave the cyclised compound 37 on treatment with sodium hydride. Further elaboration of 37 gave 38 which was catalytically hydrogenated to yield the tricyclic





compound 39. These authors intend to incorporate this ring-annulation technique evolved on the model compound into a sequence to produce lycopodine.

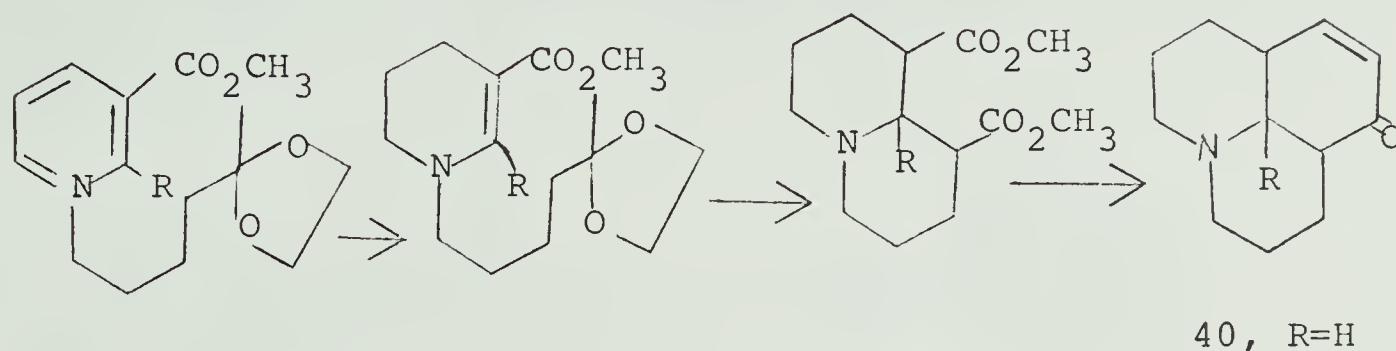


Wenkert and Stevens<sup>31</sup> have also developed a method for the construction of a substituted julolidine. The

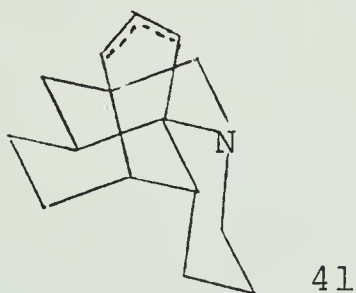




hydrojulolidine 40 was prepared as indicated. The authors propose to add the bridge ring by elaboration of an appropriate side chain R.



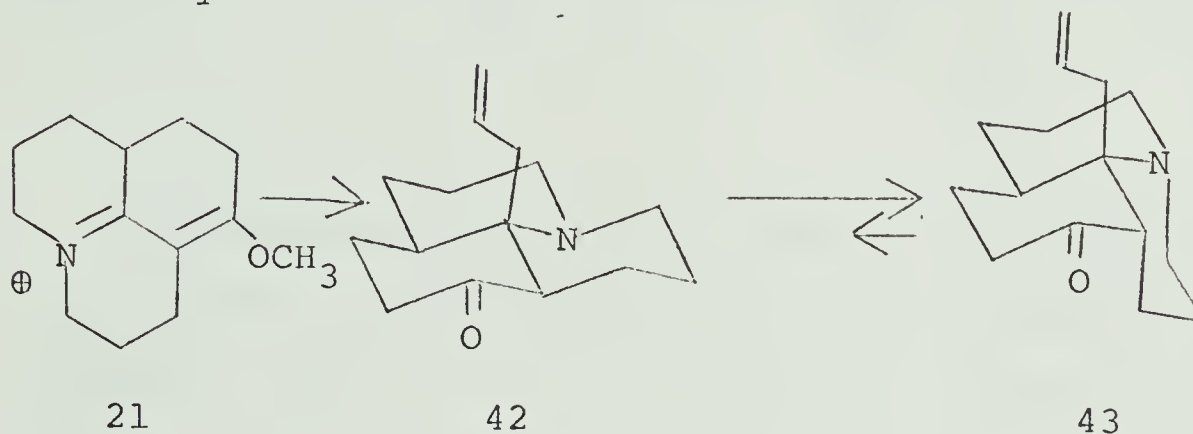
The bulk of the research on the synthesis of Lycopodium alkaloids has been published by Wiesner, Valenta and co-workers. They first reported the synthesis<sup>32</sup> of the tetracyclic compound 41 which contains all but one of the carbon atoms present in lycopodine.



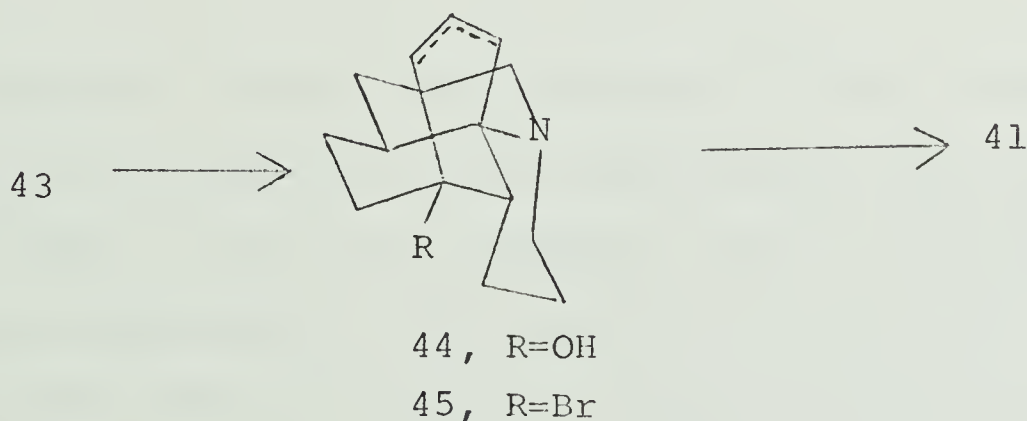
The immonium salt 21 used in the synthesis of the lyconnotine degradation product was treated with allyl magnesium bromide instead of isobutyllithium to yield the ketone 42, after hydrolysis of the intermediate enol



ether. Ketone 42 was shown to have Bohlmann bands in the infrared indicating it possessed the incorrect stereochemistry. Equilibration of 42 under basic conditions, however, gave the correct lycopodine stereochemistry 43.



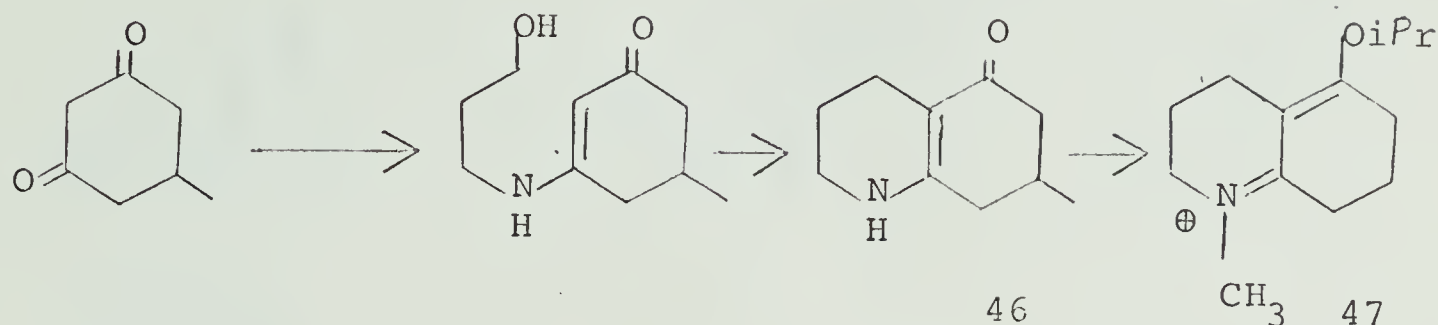
Treatment of 43 with 70% sulphuric acid gave a high yield of the ring closed compound 44 which was converted to the bromo analogue 45 by refluxing in conc. hydrobromic acid. Reduction with sodium amalgam gave the tetracyclic amine 41.



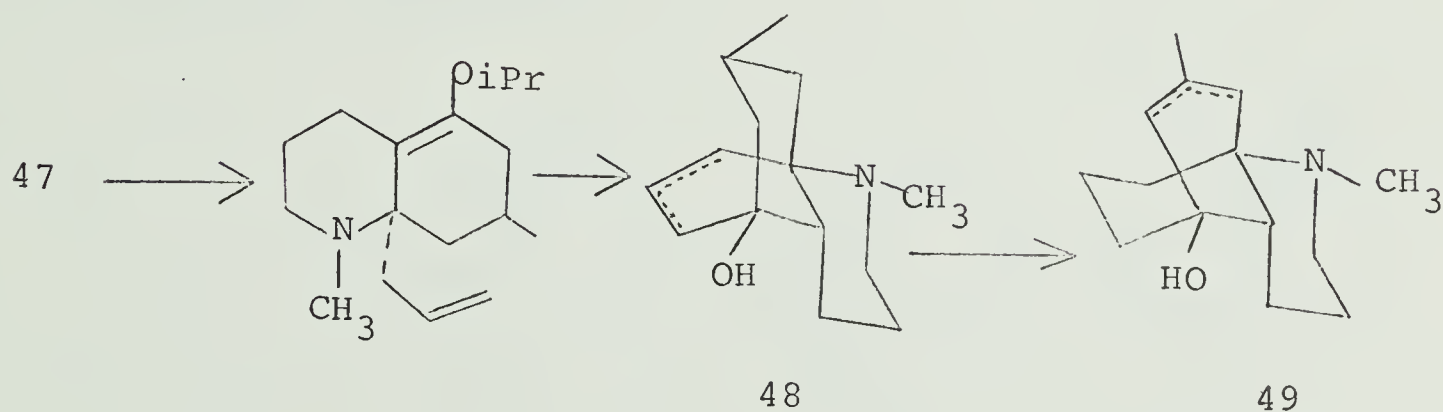
A similar approach was attempted as follows from dihydroorcinol. 3-Aminopropanol was added and cyclised to the vinylogous amide 46. Methylation and treatment with



isopropyl iodide gave the salt 47.

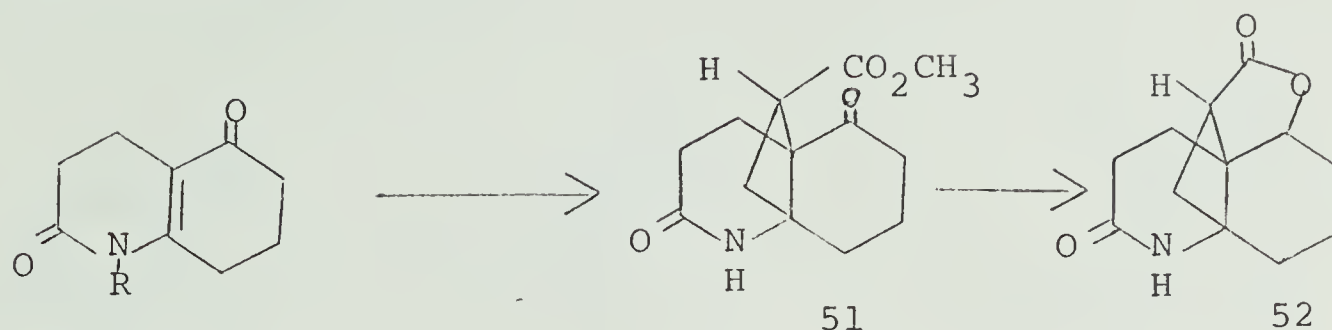


Allylmagnesium bromide was added to the immonium salt 47 as before and the product was then cyclised in 75% sulphuric acid to give 49, not 48 as expected. Alcohol 49 must have been obtained from 48 by hydride transfer.



Wiesner, Valenta and co-workers<sup>33</sup> then turned their attention to annotinine and investigated some photo-additions to form the cyclobutane ring. The amide 50 was first irradiated in ethyl acrylate to give stereospecifically the adduct 51, which on sodium borohydride reduction and hydrolysis gave lactone 52.

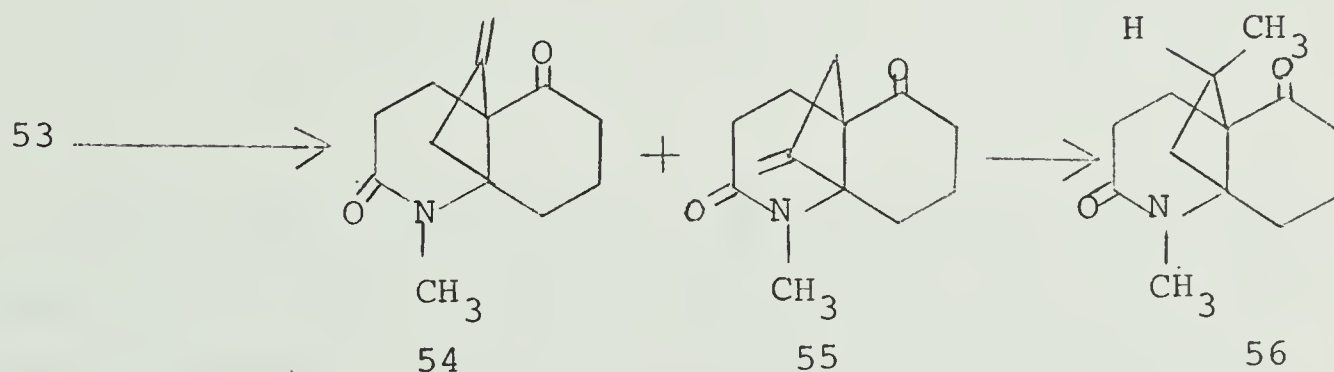




50, R=H

53, R=CH<sub>3</sub>

The amide 53 was also irradiated with allene and led to addition in both directions to give 54 and 55. Ketone 54 was reduced stereospecifically by hydrogenation of the ketal of 54. Subsequent hydrolysis of the ketal furnished 56.

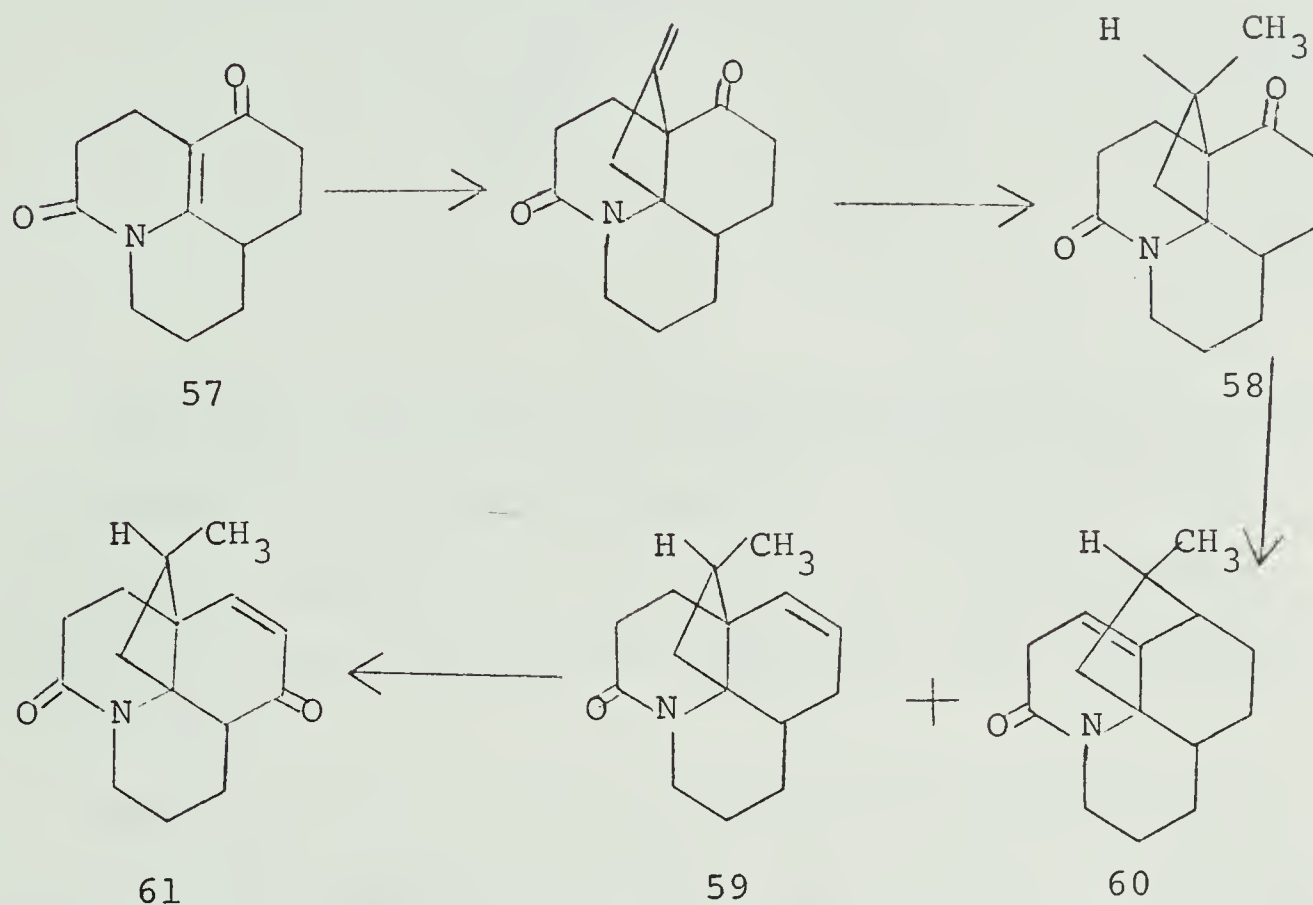


In a subsequent publication <sup>34</sup> the amide 57 gave under the same conditions, photoaddition in one direction only. The product was hydrogenated as before to yield 58, which was reduced with sodium borohydride. Mesylation and elimination using potassium cyanide in dimethylformamide gave 59 and 60. Oxidation of 59 with



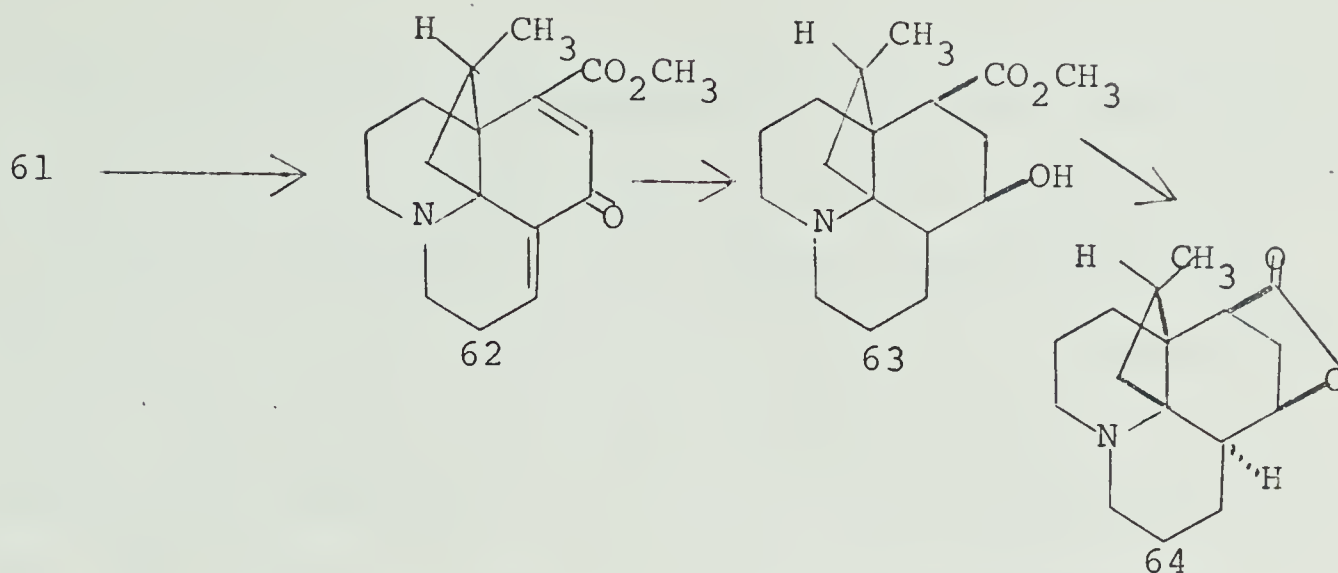


selenium dioxide gave 61.



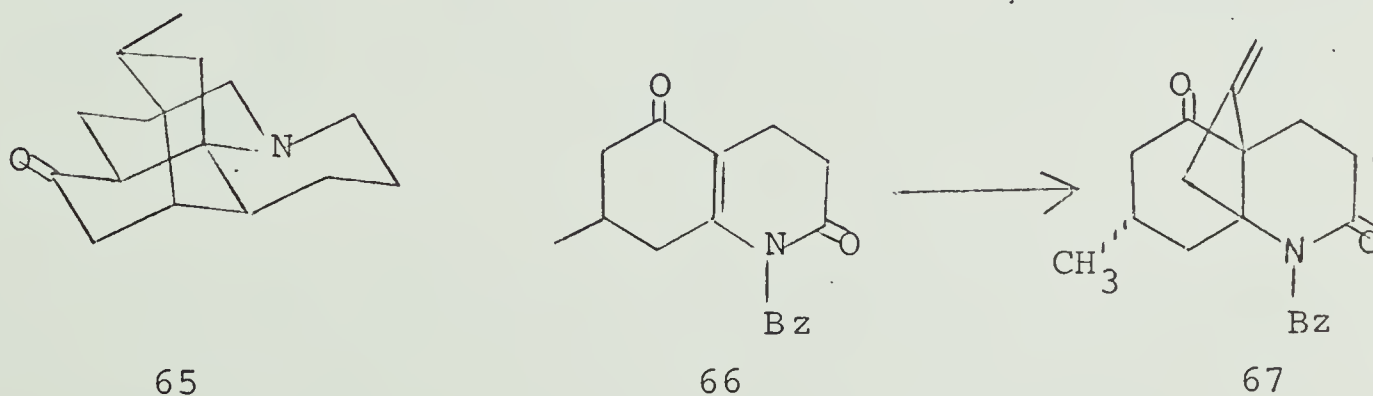
In the next publication <sup>35</sup> the authors converted the amide 61 to 62 by treatment with potassium cyanide in dimethylformamide. The nitrile formed was hydrolysed and esterified to a methyl ester. Treatment of the methyl ester with selenium dioxide gave 62, which on catalytic hydrogenation gave 63. The ester 63 was then converted to the lactone 64. Both 63 and 64 had previously been prepared by degradation of annotinine.





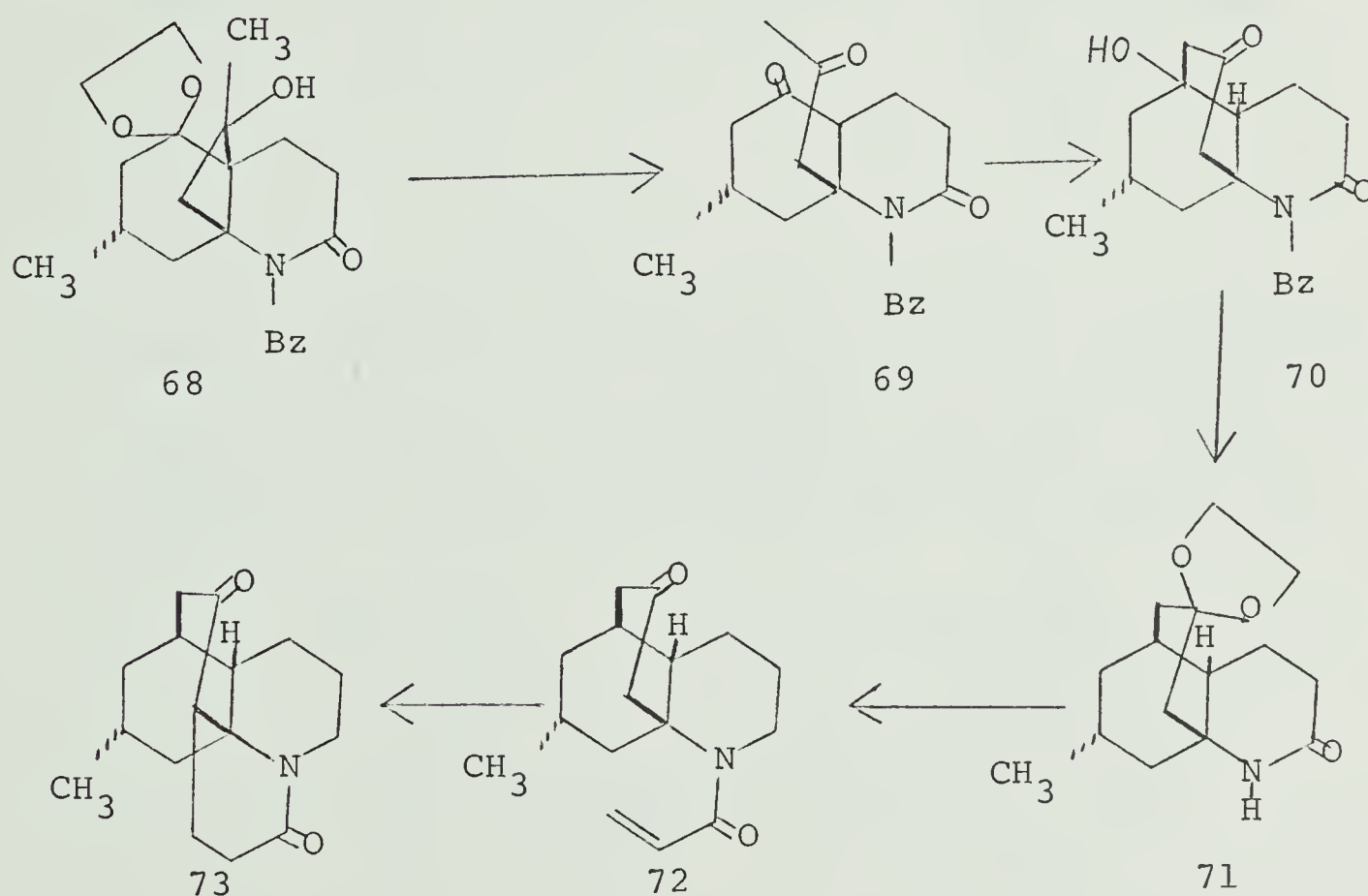
The final publication <sup>36</sup> describes the conversion of the lactone 64 into annotinine (2). This is therefore the first synthesis of a naturally occurring Lycopodium alkaloid, completed some ten years after the structural determination.

Wiesner, Valenta and co-workers have also recently synthesised epilycopodine (65), which is not a naturally occurring alkaloid, but has been described by Ayer and Iverach <sup>38</sup>, who obtained it by catalytic hydrogenation of anhydrolycodoline. This sequence again uses the allene photoaddition with the amide 66 as starting material to yield 67. Ketone 67 was ketalised, epoxidised and reduced





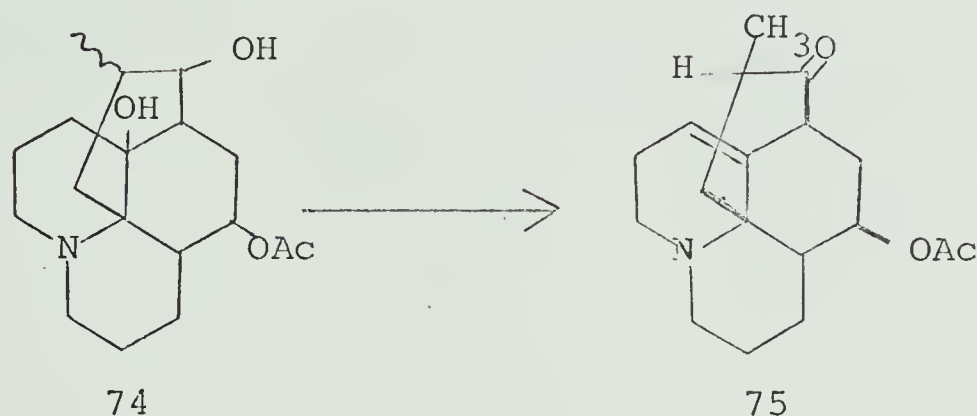
to give 68, which on acid hydrolysis gave 69. Standing in sodium hydroxide solution for three days aldolised 69 to 70, which was converted to 71. Lithium aluminum hydride reduction of 71 and then deketalisation and treatment with acrylyl chloride gave 72. Epilycopodine lactam (73) was obtained by refluxing 72 in toluene with p-toluenesulphonic acid. The lactam 73 was converted to dl-epilycopodine by lithium aluminum hydride reduction followed by Jones oxidation.



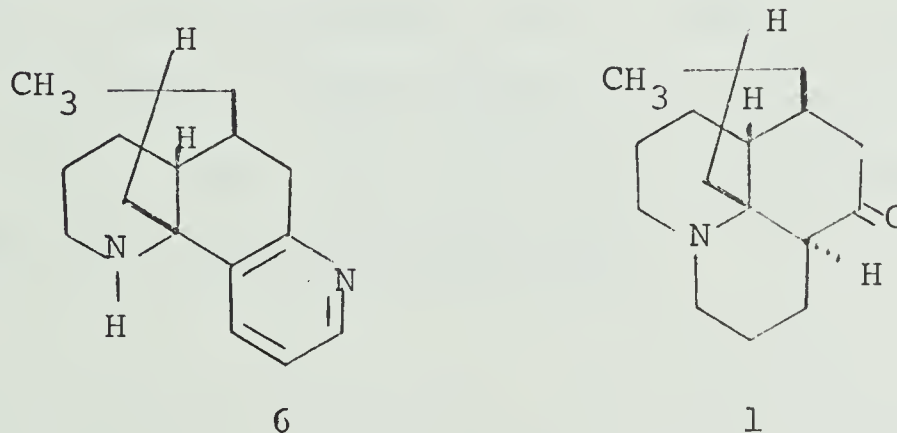


The present work consists of three different sections which are outlined briefly below.

1. The elucidation of the structure of lycofawcine (base L) (74), and its conversion to O-acetylacrifoline (75) as a proof of the structure. This part was carried out and completed in 1964.



2. The total synthesis of lycodine (6) was attempted but was not brought to a successful conclusion. This research was carried out in 1964 and until March 1965.

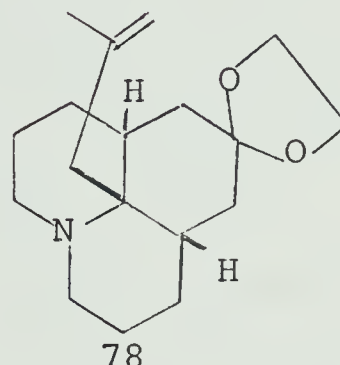
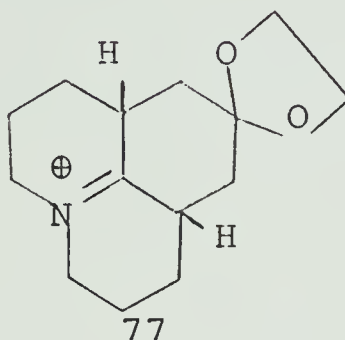
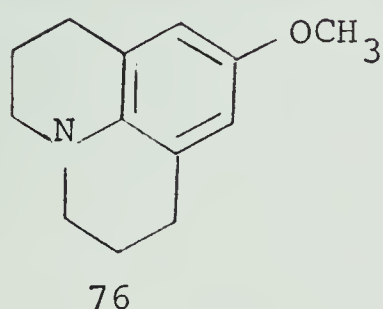


3. The total synthesis of lycopodine (1) was continued and completed. Earlier research<sup>39</sup> in these laboratories had progressed from simple starting materials





to the substituted julolidine 76. The julolidine 76 had been reduced and converted to an immonium salt 77. Grignard addition had given a cis-cis hexahydrojulolidine derivative 78. These steps were improved to obtain better yields.



The cis-cis hexahydrojulolidine was converted into a cis-trans hexahydrojulolidine, the side chain was suitably functionalised, the nitrogen blocked, and ring closure brought about. This work was initiated in April 1965 and completed in early December, 1967. Much of the synthetic work described in the introduction appeared during the course of this work. The synthesis of annotinine appeared after this work was completed.



## Discussion and Results

### Part 1.

#### The Elucidation of the Structure of Lycofawcine (Base L).

Lycofawcine (base L) was first isolated by Burnell<sup>40</sup> and co-workers from Lycopodium Fawcettii, along with several other alkaloids, amongst which was base O, which was found to be acetyl-base L. Preliminary results<sup>40</sup> showed base L to possess the empirical formula  $C_{18}H_{31}NO_4$ . Base L is readily hydrolysed to a trihydroxy compound, desacetyl-base L,  $C_{16}H_{29}NO_3$ , which does not consume periodic acid, indicating that it does not contain an  $\alpha$ -glycol system. Acetylation of desacetyl-base L at room temperature gives rise to a diacetate, Base O, but at lower temperature (5°) a monoacetate is obtained. This compound is not identical with base L and must therefore be a positional isomer, called isobase L, since on further acetylation base O is afforded.<sup>40</sup> A similar sequence has been noted with lycofoline.<sup>41</sup> This suggested the presence of secondary axial and equatorial hydroxyl groups.<sup>40</sup> Further acetylation of base O did not give a triacetate suggesting that the third hydroxyl group is tertiary. This assumption was further strengthened by the chromium trioxide oxidation of base L to a hydroxyketo-acetate,  $C_{18}H_{29}NO_4$ . Dehydro-base L was easily hydrolysed to a dihydroxyketone, desacetyldehydro base L,  $C_{16}H_{27}NO_3$ , whose infrared absorption



indicated a ketone in a six or larger membered ring.

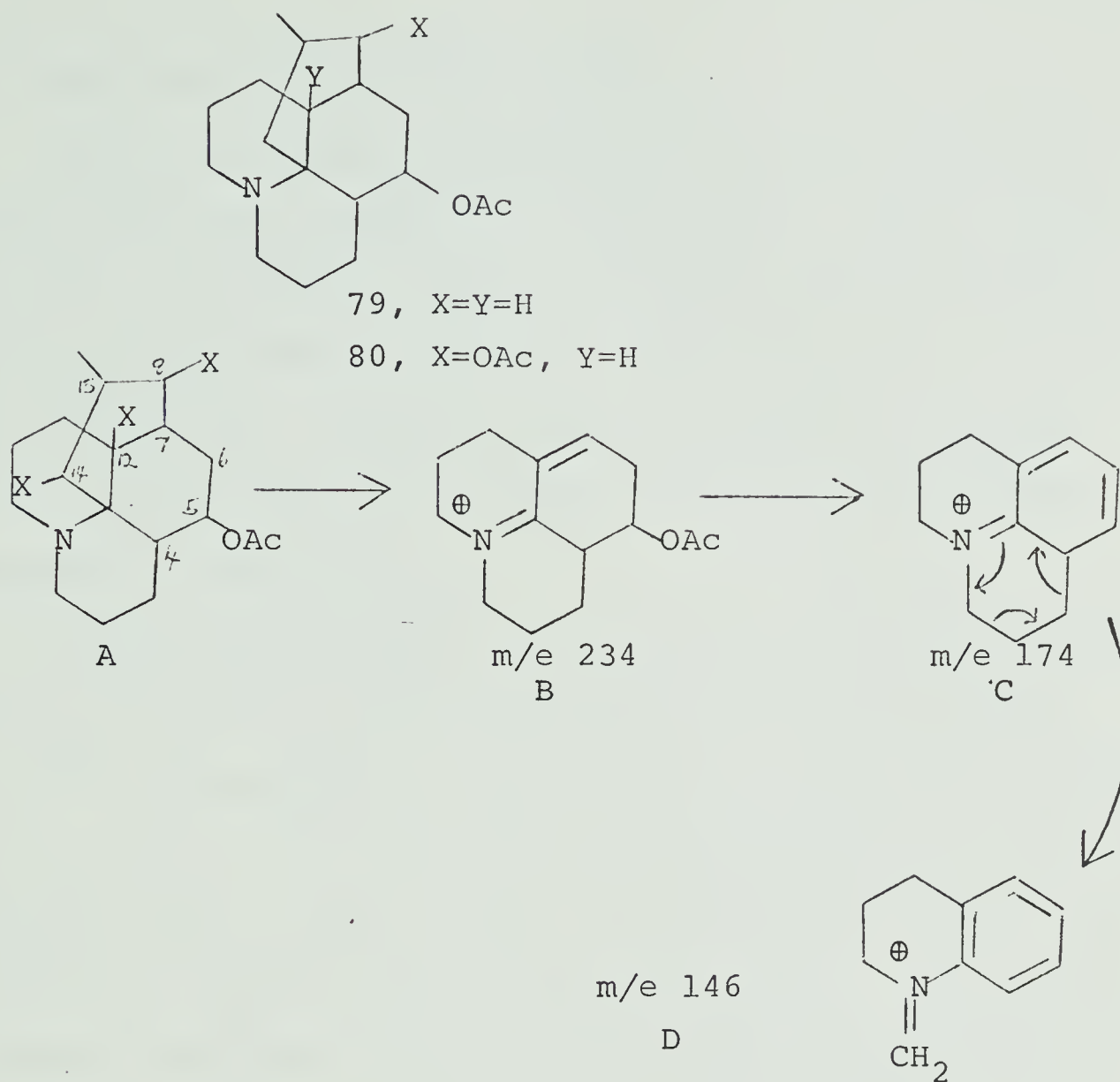
Base L formed a monomethiodide, mp 281-282°, which analysed for  $C_{18}H_{31}NO_4 \cdot CH_3I$ .

A summary of the information <sup>40</sup> shows base L to be a tricyclic tertiary amine, possessing a tertiary hydroxyl, a secondary equatorial hydroxyl, and a secondary axial O-acetyl group. For ease of reference we have suggested the trivial name lycofawcine for base L, and correspondingly acetyllycofawcine for base O.

In the present research the mass spectra of lycofawcine, acetyllycofawcine, desacetyllycofawcine, dehydrolycofawcine, and desacetyldehydrolycofawcine were measured. The first fact apparent was that the molecular formula originally suggested for lycofawcine,  $C_{18}H_{31}NO_4$  (mol. wt. 325), should be changed to  $C_{18}H_{29}NO_4$  (mol. wt. 323). This then requires that the base be tetracyclic and not tricyclic.

The mass spectra of lycofawcine, acetyllycofawcine, and dehydrolycofawcine all show strong peaks at m/e 234, 174 and 146. This fragmentation pattern is characteristic of Lycopodium alkaloids of the lycopodine type with a  $C_{12}$  O-acetyl group such as O-acetyldihydrolycopodine (79) <sup>42</sup> and O-acetyllofoline (80) <sup>43</sup> as shown in scheme 1.





Scheme 1.

The two desacetyl compounds, desacetyllycofawcine and desacetyldehydrolycofawcine show a peak at m/e 192 (base peak) which corresponds to fragment B with hydroxyl in place of acetyl. They also show peaks at m/e 174 and m/e 146, corresponding to fragments C and D. The desacetyl compounds have their base peak at m/e 192 rather than at m/e 174 as in the acetyl compounds. This is explained by the fact that elimination of water does not take place





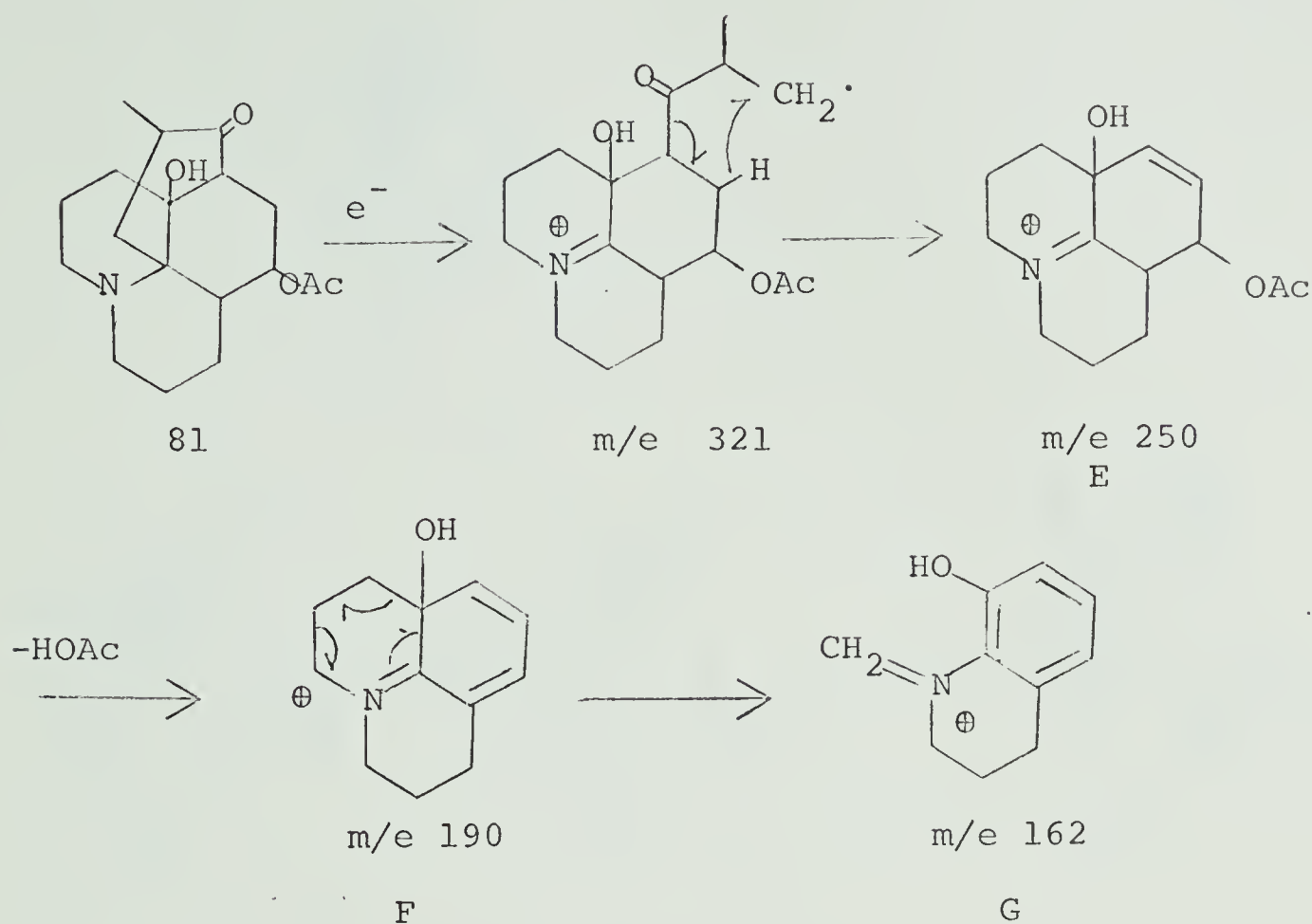
as readily as loss of acetic acid.

The two hydroxyl groups must then be placed in two of the positions marked X in structure A. C<sub>15</sub> is ruled out since the nuclear magnetic resonance (nmr) spectrum of dehydrolycofawcine shows a C-methyl doublet at  $\tau$  8.74. This means that a hydrogen must be present on C<sub>15</sub> and also suggests that the carbonyl function in the dehydro compound is at C<sub>8</sub> or C<sub>14</sub>.

A decision between the positions of the keto function at C<sub>8</sub> or C<sub>14</sub> can be made by application of the octant rule<sup>44</sup>. As predicted if the ketone is at C<sub>8</sub>, the optical rotatory dispersion curve for dehydrolycofawcine would show a negative Cotton effect curve. If the ketone were at C<sub>14</sub>, a positive Cotton effect would be expected. The optical rotatory dispersion curves will be discussed further below.

The second hydroxyl group has been designated to C<sub>12</sub>. If the hydroxyl group were at C<sub>14</sub>, facile dehydration to an  $\alpha,\beta$ -unsaturated ketone in dehydrolycofawcine would be expected, and this does not occur. Further evidence for the placing of the hydroxyl at C<sub>12</sub> comes from the mass spectrum of dehydrolycofawcine (81) as shown in scheme 2. Acetyllycofawcine shows the same fragments E, F, and G. The mass spectrum of desacetyldehydrolycofawcine also shows fragments E (m/e 208, OH in place of OAc) and F.



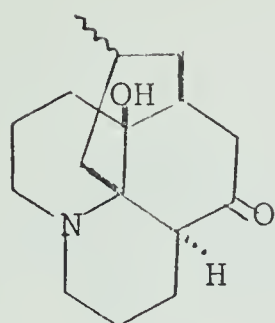


Scheme 2

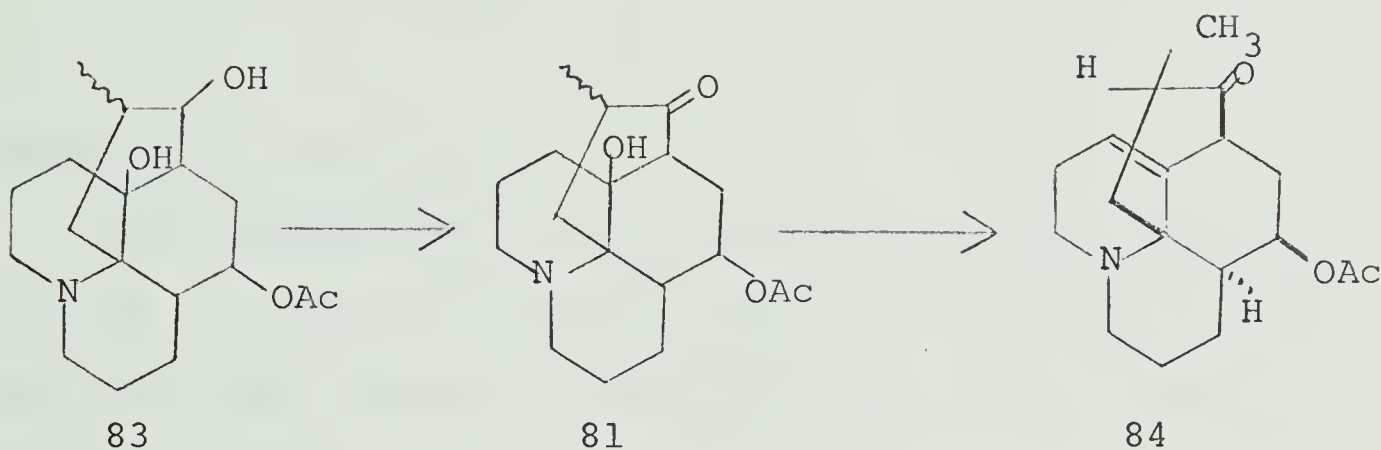
All other peaks in the mass spectra can be accounted for by loss of hydroxyl, water, acetoxyl or acetic acid. The one discrepancy in the mass spectrum is that lycodoline (82)<sup>42</sup> does not give a ready loss of the bridge ring as occurs in all the lycofawcine compounds. From this data the structure (83) was deduced for lycofawcine.

In order to confirm the structural assignment a correlation with a known compound was desirable. The most obvious choice was to dehydrate dehydrolycofawcine (81) to O-acetylacrifoline (84). Dehydration using phosphorus pentoxide was unsuccessful but phenylphosphoric dichloride<sup>38</sup>





82



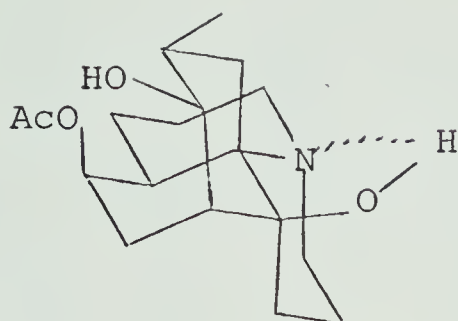
83

81

84

gave O-acetylacrifoline<sup>45</sup> in good yield. Since the stereochemistry of O-acetylacrifoline is known this result also establishes the stereochemistry of lycofawcine except at C<sub>8</sub>, C<sub>12</sub> and C<sub>15</sub>. Dehydrolycofawcine (81), like lycodoline (82) has an intramolecularly hydrogen bonded hydroxyl group (concentration independent band at 3565 cm<sup>-1</sup> in the infrared spectrum (CCl<sub>4</sub> solution)), and since none of the lycofawcine compounds show Bohlmann bands,<sup>46</sup> characteristic of trans-quinolizidines, the stereochemistry at C<sub>12</sub> must be the same as in lycodoline (82) and as shown in the conformational drawing (85). The configuration at C<sub>8</sub> is based on the earlier suggestion<sup>40</sup> that the secondary





85

hydroxyl is equatorial.

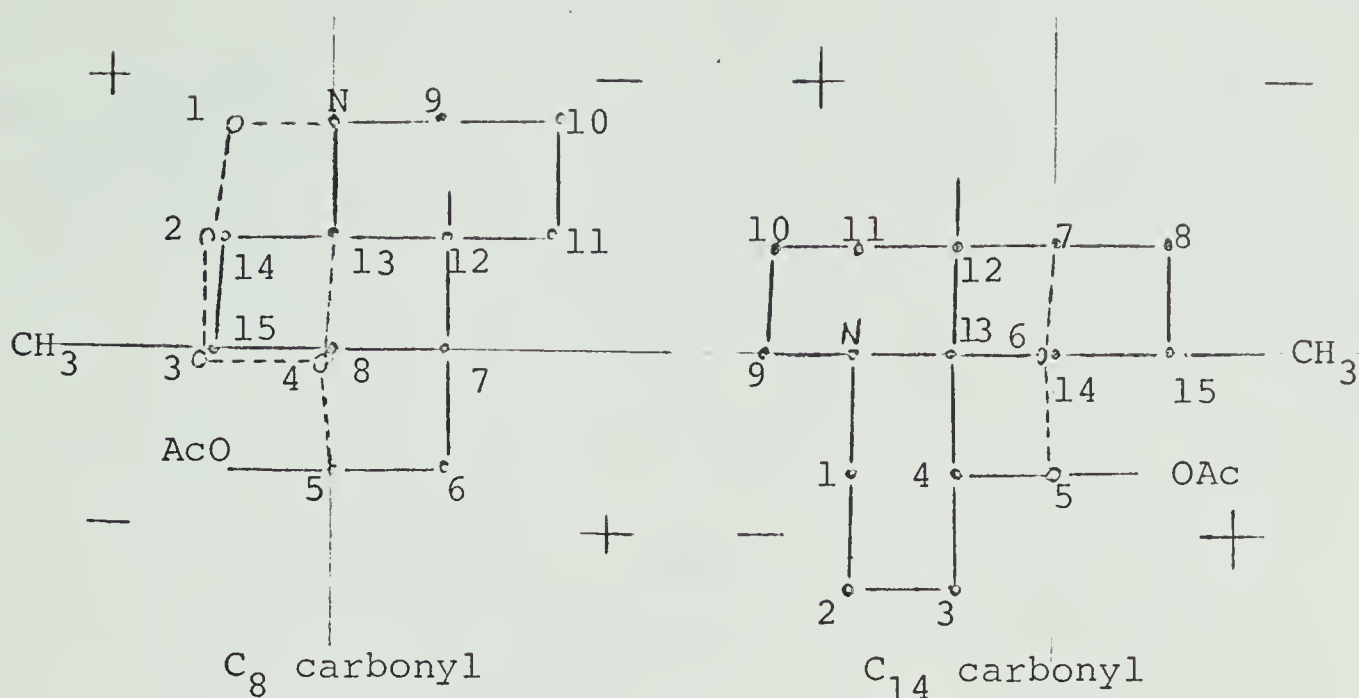
The configuration at  $C_{15}$  is assigned on the basis of analogy with other Lycopodium alkaloids which have, except in cases where there is a carbonyl group at  $C_8$ , the configuration shown.

Optical rotatory dispersion was used to decide between  $C_{14}$  and  $C_8$  for the carbonyl group. The octant diagrams are shown below. The  $C_8$  carbonyl clearly would show a negative Cotton effect while the  $C_{14}$  carbonyl compound probably would show a positive effect.

There is the possibility that the Cotton effect could also be used to assign the stereochemistry at  $C_{15}$  more accurately. O-Acetylacrifoline (84) has the bridge ring in a boat conformation with the opposite stereochemistry for the methyl group. O-Acetylacrifoline (84) has a strong negative Cotton effect ( $\alpha = -200$ ), however it is a  $\beta, \gamma$ -unsaturated ketone. Fawcettiine (86)<sup>21</sup> is oxidised without epimerisation to dehydrofawcettiine (87).

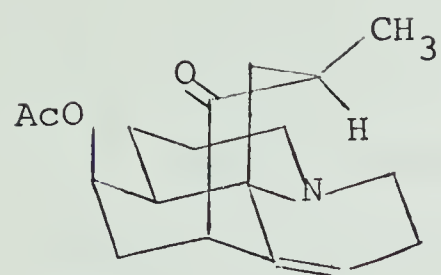




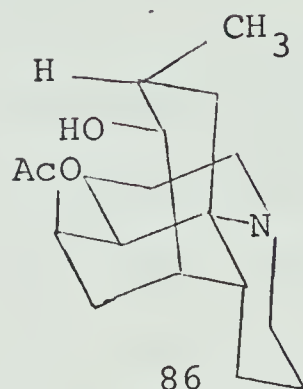


Dehydrofawcettiine, which has a similar structure to dehydrolycofawcine has the bridge ring in a boat conformation and a negative Cotton effect ( $a = -50$ ). Dehydrofawcettiine is however easily epimerised to annofoline (88) in base.<sup>21</sup> O-Acetylannofoline (89) also has a negative Cotton effect ( $a = -48$ ). These two compounds have both possible bridge ring conformations with similar Cotton effects. No deductions can therefore be made concerning dehydrolycofawcine until such time as further studies are made. It is possible that all three exist in twist forms, giving a similar Cotton effect.

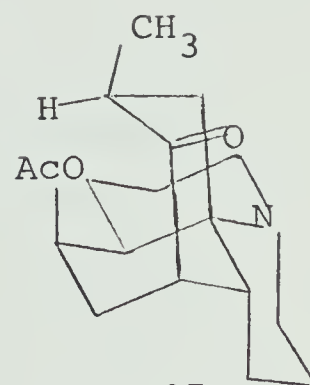




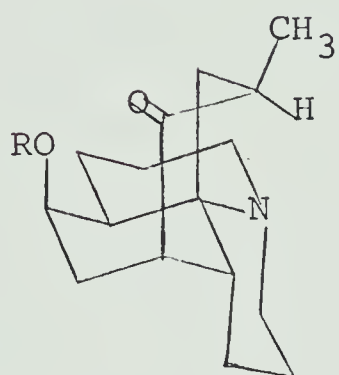
84



86



87



88,  $\text{R}=\text{H}$

89,  $\text{R}=\text{Ac}$



## Experimental

### Part 1

Optical Rotatory dispersion spectra were measured on a Rudolph Automatic Recording Spectropolarimeter. Nuclear magnetic resonance (nmr) spectra were measured on a Varian Associate Model HR-100 spectrometer with tetramethylsilane as an internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 421 dual grating infrared spectrometer. Mass spectra were determined on an A.E.I. Model MS-2H mass spectrometer. Melting points were determined on a Fisher-John melting point apparatus and are uncorrected. The alumina used was BDH basic alumina of activity III-IV (Brockmann scale). The alumina used for thin layer chromatography (tlc) was Research Specialty Company aluminum oxide G.

#### The Structural Determination of Lycofawcine.

##### Purification of Crude Lycofawcine.

The crude hydroperchlorate (548 mg), obtained from R. H. Burnell <sup>40</sup>, was dissolved in water (50 ml), basified with 10% ammonium hydroxide solution, and extracted with chloroform (50 ml, five times). The organic extract was dried ( $\text{MgSO}_4$ ) and evaporated to a gum. Tlc showed two components which were separated by column chromatography on alumina. Elution with ether (6 fractions of 25 ml)



gave pure fawcettiine (138 mg): mp 168 - 170° (reported 170 - 171°), ir spectrum identical with an authentic sample. Further elution with ether (7 fractions of 25 ml) gave mixed fractions. Elution with chloroform (10 fractions of 25 ml) gave pure lycofawcine (200 mg): non-crystalline; ir ( $\text{CHCl}_3$ ) 1220, 1760  $\text{cm}^{-1}$  (acetate), 3520, 3610  $\text{cm}^{-1}$  (OH); mass spectrum (200°, heated inlet) m/e (rel. intensity) 323(2), 263(14), 245(42), 234(50), 174(100), 172(81), 146(38), 144(25).

#### Dehydrolycofawcine.

Lycofawcine (124.6 mg, 0.39 mmoles) was dissolved in dry pyridine (3 ml) and added to a cold stirred slurry of chromium trioxide (600 mg) in pyridine (3 ml). The mixture was stirred for 15 minutes at 0°, one hour at room temperature, and then kept for two hours in the refrigerator. The reaction mixture was poured into water (50 ml) and basified with conc. ammonium hydroxide solution. The solution was extracted with chloroform (50 ml, five times), dried ( $\text{MgSO}_4$ ), and evaporated to a crystalline solid (104.5 mg, 0.33 mmoles, 85%): tlc identical with authentic material supplied by R. H. Burnell; ir (nujol) 1235, 1735  $\text{cm}^{-1}$  (acetate), 1695  $\text{cm}^{-1}$  (C=O), 3020  $\text{cm}^{-1}$  (OH); ( $\text{CCl}_4$ ) 1220, 1736  $\text{cm}^{-1}$  (acetate), 1703  $\text{cm}^{-1}$  (C=O), 3565  $\text{cm}^{-1}$  (concentration independent, intramolecularly H-bonded OH); nmr ( $\text{CDCl}_3$ )  $\tau$  8.74 (3H, d,  $J = 6$  cps,  $\text{CH}-\text{CH}_3$ ), 8.02 (3H, s,  $\text{OCOCH}_3$ ), 4.97 (1H, q,  $\text{CHOAc}$ );





optical rotatory dispersion in methanol. (c 0.10)  $[\phi]_{589}^-$  190°,  $[\phi]_{400}$  - 475°,  $[\phi]_{305}$  - 2025°,  $[\phi]_{260}$  + 825°; mass spectrum (200°, heated inlet), m/e (rel. intensity) 321(14), 304(7), 262(17), 250(51), 234(100), 190(16), 174(53), 162(18), 146(18).

Dehydration of Dehydrolycofawcine.

A. Phosphorus Pentoxide. Dehydrolycofawcine (10 mg) and phosphorus pentoxide (100 mg) were refluxed in toluene (6 ml) for four hours under anhydrous conditions. Water (50 ml) was slowly added and the solution poured into 1 N hydrochloric acid (50 ml) and chloroform (75 ml). The organic layer was extracted with more 1 N hydrochloric acid (50 ml, three times). All the acidic extracts were combined and basified with conc. ammonium hydroxide solution. The basic solution was extracted with chloroform, dried ( $\text{MgSO}_4$ ), and evaporated to a gum (6 mg). Tlc showed some starting material, a trace of O-acetylacrifoline and a major nonpolar component. Longer reaction time resulted in the disappearance of all the starting material but did not increase the amount of O-acetylacrifoline.

B. Phenylphosphoric Dichloride. Dehydrolycofawcine (55 mg, 0.17 mmoles) was heated at 65° in a 1:1 solution of phenylphosphoric dichloride: pyridine (6 ml) for 20 hours. The excess phenylphosphoric dichloride was destroyed by the slow addition of ice. The reaction mixture was basified



with sodium hydroxide and extracted with chloroform (50 ml, five times). The chloroform extract was dried ( $\text{MgSO}_4$ ) and evaporated to an oil (40 mg). Tlc indicated mainly O-acetylacrifoline with some dehydrolycofawcine. The two components were separated by column chromatography. Elution with ether-chloroform (7:3) yielded crystalline O-acetylacrifoline (25 mg, 0.08 mmoles, 50%) identical (ir, tlc, mixed mp undepressed) with authentic material.

The methiodide, prepared in methanol, and recrystallised from acetone-ether melted at  $278 - 279^\circ$ . When admixed with an authentic sample of O-acetylacrifoline methiodide, mp  $281 - 282^\circ$ , it melted at  $280 - 281^\circ$ .

The following compounds were supplied by R.H. Burnell.

Dehydrodesacetyllycofawcine: Nmr ( $\text{CD}_3\text{SOCD}_3$ )  $\tau$  9.0 (3H, d,  $J = 6$  ps,  $\text{CH}-\text{CH}_3$ ); mass spectrum ( $200^\circ$ , heated inlet) m/e (rel intensity) 279(4), 262(6), 208(16), 192(100), 175(25), 174(29), 146(14).

Acetyllycofawcine (Base O): Mass spectrum ( $200^\circ$ , heated inlet) m/e (rel. intensity) 365(15), 348(14), 306(100), 250(20), 246(55), 234(20), 228(25), 190(25), 174(45), 162(20), 146(40).

Desacetyllycofawcine: Mass spectrum ( $200^\circ$ , heated inlet) m/e (rel. intensity) 281(3), 264(6), 208(8), 192(100), 174(18), 146(8).



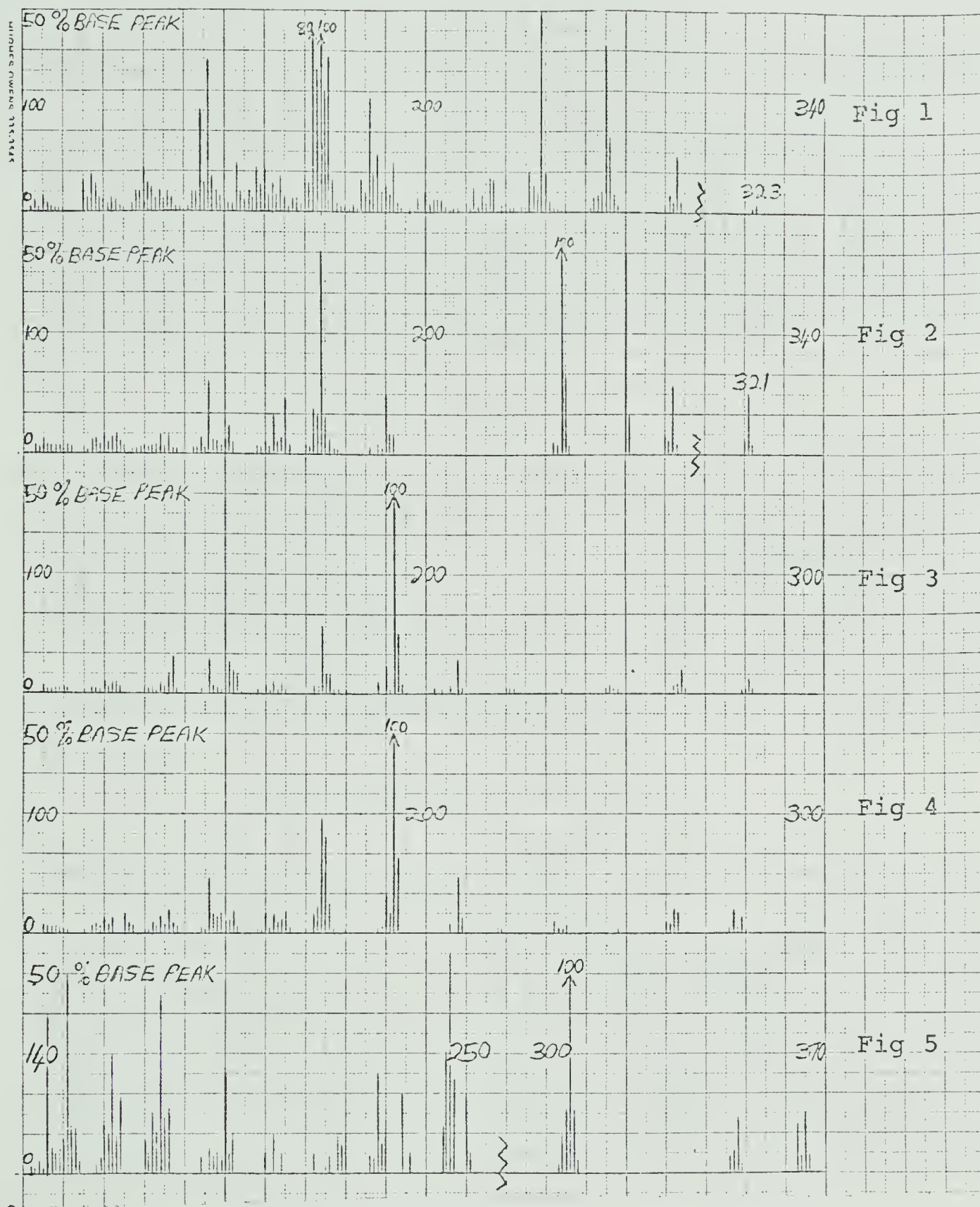


Fig. 1 Lycofawcine. Fig. 2 Dehydrolycofawcine. Fig. 3 Desacetyllycofawcine. Fig. 4 Desacetyldehydrolycofawcine  
Fig. 5 Acetyllycofawcine





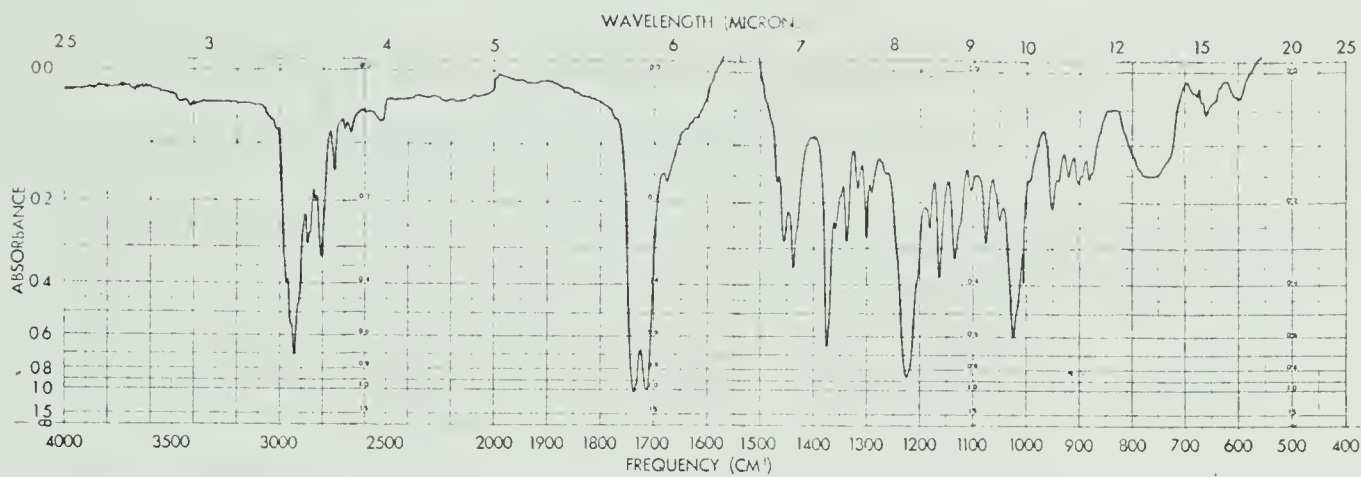


Fig. 6 O-Acetylacrifoline

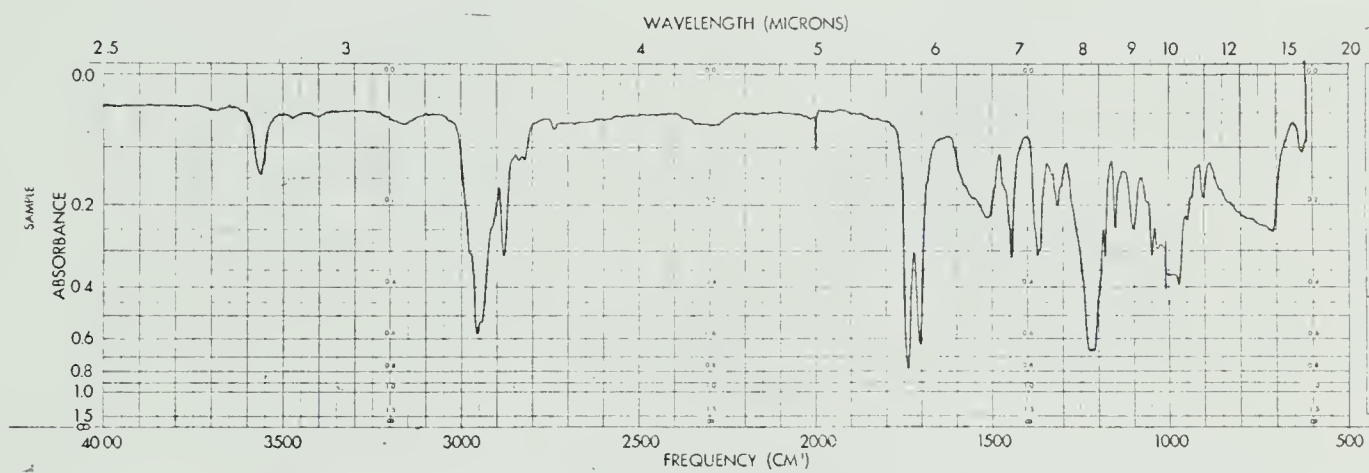


Fig. 7 Dehydrolycofawcine

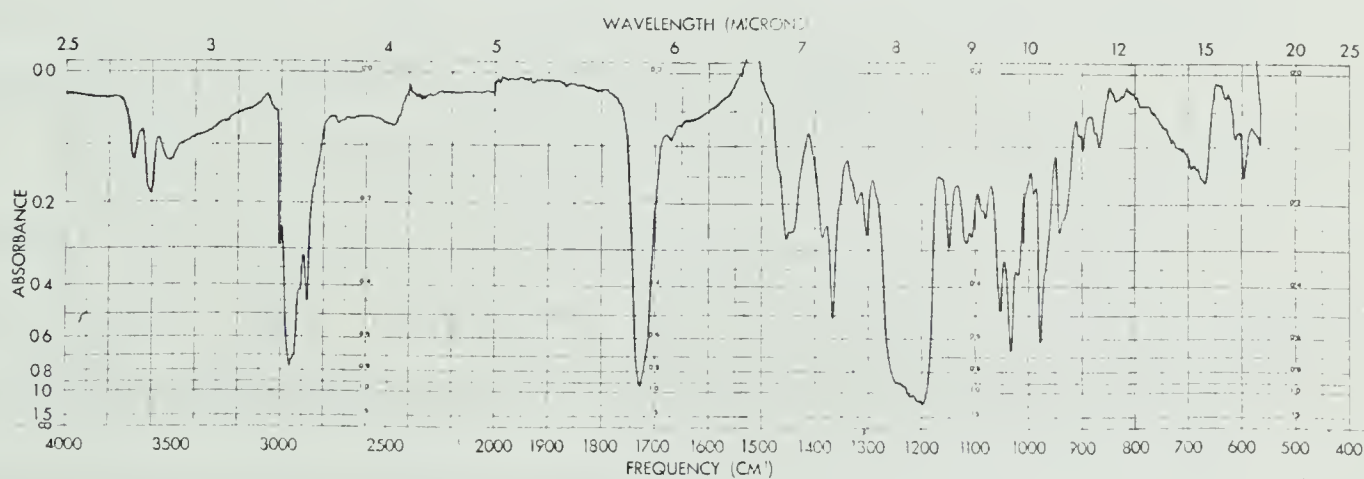


Fig. 8 Lycofawcine



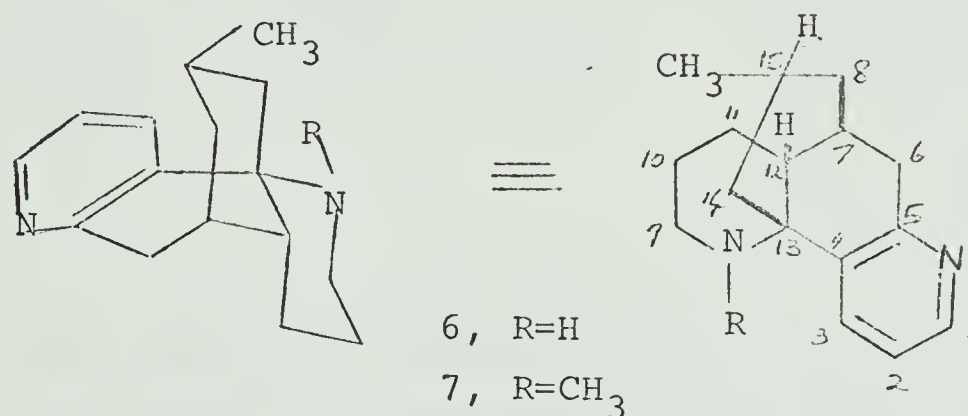


## Discussion and Results

### Part 2

#### The Attempted Synthesis of Lycodine.

Lycodine was first isolated from Lycopodium Annotinum L. in 1958 by Anet and Eves.<sup>47</sup> N-Methyllycodine was also isolated from the same plant.<sup>6</sup> The structures of lycodine (6) and N-methyllycodine (7) are shown below.



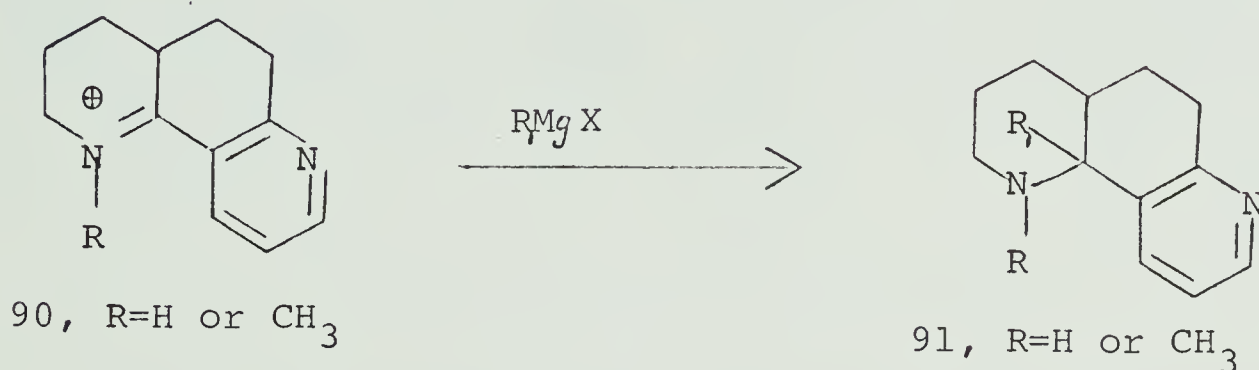
These two alkaloids, along with  $\alpha$ -obscurine,  $\beta$ -obscurine and several other alkaloids form the di-nitrogenous tetracyclic group of Lycopodium alkaloids.

Lycodine and N-methyllycodine are the only two Lycopodium alkaloids containing a pyridine ring in their structure. This structural feature should simplify their synthesis compared to that of other Lycopodium alkaloids by requiring only three rings to be stereospecifically elaborated.

It is well known that immonium salts are readily attacked by nucleophilic alkylating agents. Leonard<sup>48</sup>



has shown that Grignard reagents react particularly well with immonium salts. It was felt that this method could be successfully incorporated into the synthesis of lycodine, as a means of introducing the bridging ring into a tricyclic immonium salt such as 90.



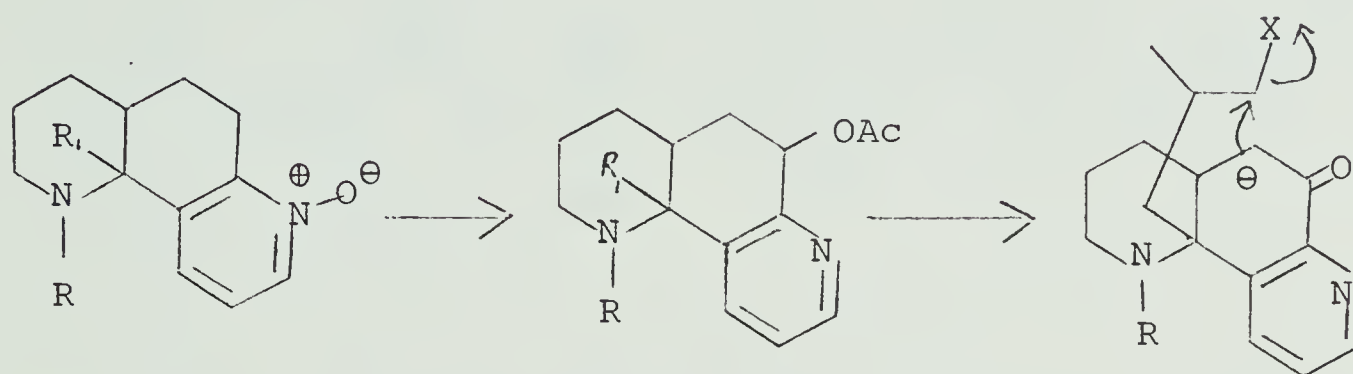
The side chain ( $\text{R}_1$  in 91) introduced by means of the Grignard addition to the immonium salt 90 would have to be further elaborated to provide a functional group which would allow ring closure on  $\text{C}_7$  to form the fourth ring. The Grignard reagent chosen would have to possess the four carbons required for the bridge ring as well as a suitable functionality for further elaboration to allow ring closure.

In order to obtain ring closure on  $\text{C}_7$  a further functional group would have to be introduced into the tricyclic ring skeleton.

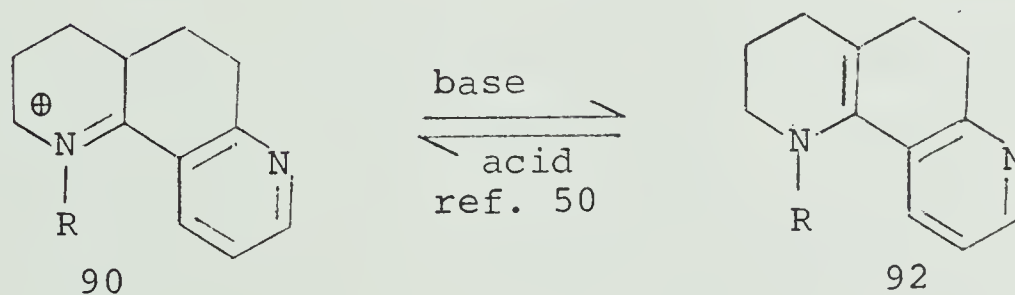
A carbon  $\alpha$  to the pyridine ring (as in  $\alpha$ -picoline) is particularly reactive and is able to undergo several substitution reactions. One such reaction<sup>49</sup> which could



be incorporated into the synthesis is outlined below. A method that could be used for ring closure, i.e. nucleophilic attack of an active methylene group to displace a suitable leaving group is also shown.



The first obstacle to be overcome was the preparation of the tricyclic immonium salt 90 or the corresponding enamine 92, and for this purpose the ketone 93 appeared to

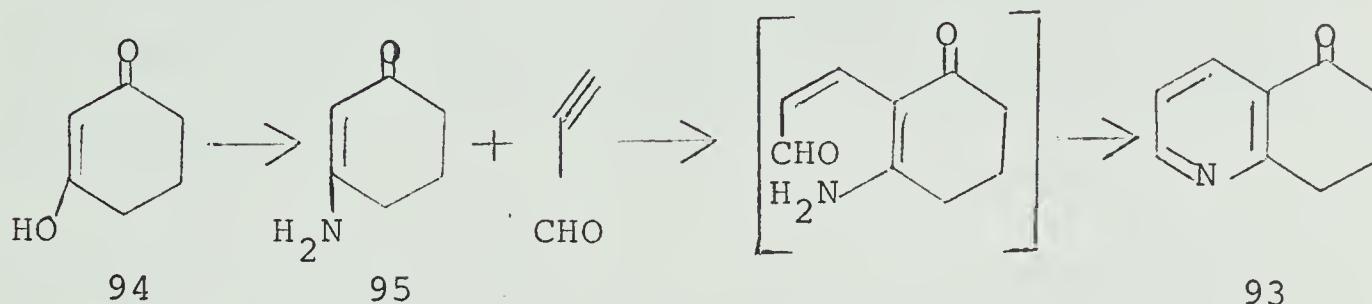


be a good starting point.

A survey of the literature revealed a suitable method<sup>51a</sup> for its preparation, which is outlined below. 1,3-Cyclohexadione (94) was treated with ammonia in benzene to give 1-aminocyclohex-1-en-3-one (95) in good yield. The 1-amino-



cyclohex-1-en-3-one was treated with propynal to give 7,8-dihydro-5(6H)-quinolone. 1,3-Cyclohexadione was first prepared by reduction <sup>52a</sup> of resorcinol with hydrogen and Raney nickel but commercial material was later used.



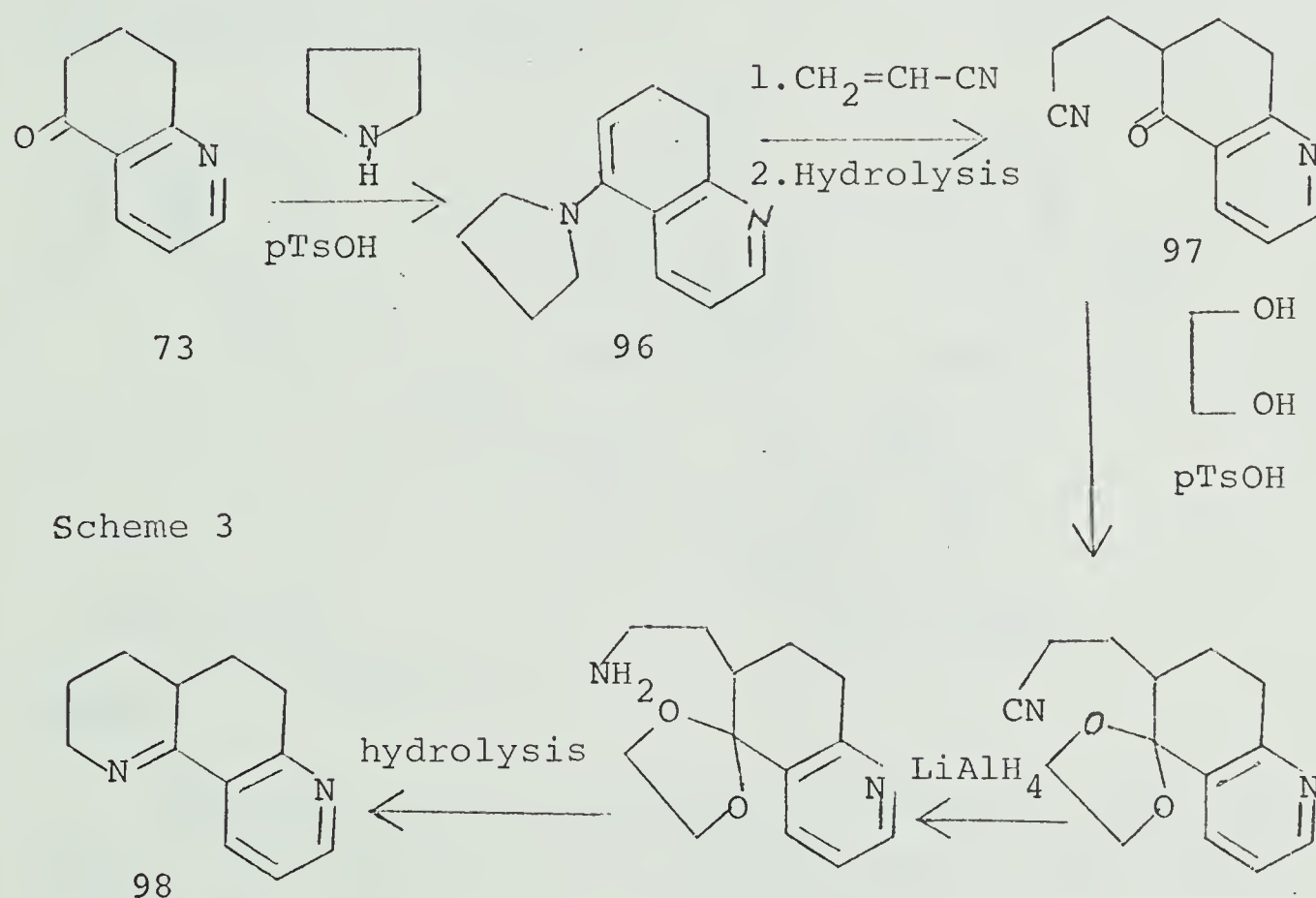
As all the intermediates in this synthesis contain a pyridine ring, a comment on the ultraviolet and nmr spectra will be useful at this stage. The ultraviolet spectrum shows two absorption bands. The first is the electron transfer band for a group such as carbonyl, imine or enamine conjugated with the pyridine ring, which absorbs at approximately 230-240 mμ. The second band is the local excitation of the pyridine ring (band II,  $\pi \rightarrow \pi^*$ ) which occurs between 265-275 mμ. This absorption is somewhat above the pyridine band II (257 mμ), but this is due to a bathochromic shift caused by alkyl substitution. The electron transfer band is not apparent when there is no chromophore other than the pyridine ring. The nmr spectrum shows absorptions for the  $\alpha$ ,  $\beta$  and  $\gamma$  protons which are present. Each proton appears as a quartet with the





following coupling constants;  $J_{\alpha\beta} = 5$  cps,  $J_{\alpha\gamma} = 2$  cps, and  $J_{\beta\gamma} = 8$  cps. The chemical shifts appear at the usual values <sup>53</sup> except when shifted downfield by the electron withdrawing carbonyl and imine groups.

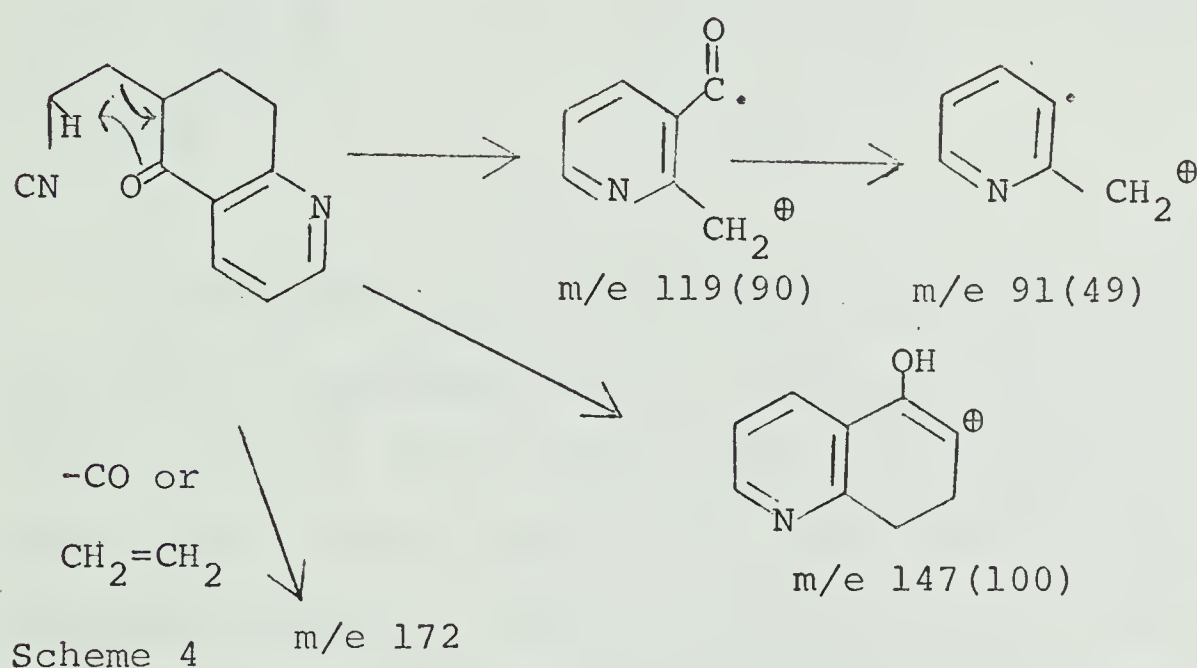
The next stage of the synthesis was the addition of the third ring. The first method <sup>54</sup> attempted is shown in scheme 3.



The pyrrolidine enamine 96 was prepared in the usual manner by refluxing the ketone with pyrrolidine in toluene using a Dean-Stark water separator. *p*-Toluenesulphonic acid was used as catalyst. The infrared spectrum of the enamine showed absorption at  $1620\text{ cm}^{-1}$  corresponding to



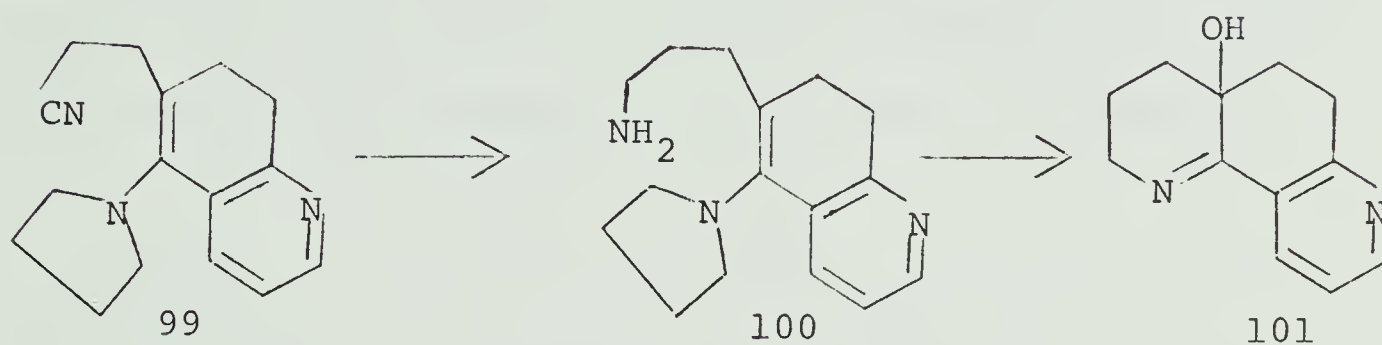
the enamine double bond, and absorption at  $\tau$  4.8 in the nmr spectrum for the olefinic proton. Reaction of the enamine with acrylonitrile and then hydrolysis gave the ketone 97 in good yield as fine colourless crystals. The structure was confirmed by infrared, with absorption at  $1682\text{ cm}^{-1}$  for the ketone and  $2250\text{ cm}^{-1}$  for the nitrile, and by nmr. The mass spectral fragmentation pattern is illustrated in scheme 4.



The next step in the projected sequence, which involved the formation of an ethylene ketal, could not be accomplished. The normal method, involving heating the ketone with ethylene glycol in benzene in the presence of *p*-toluenesulphonic acid did not work. More forcing conditions using boron trifluoride-etherate as catalyst, were also not successful.



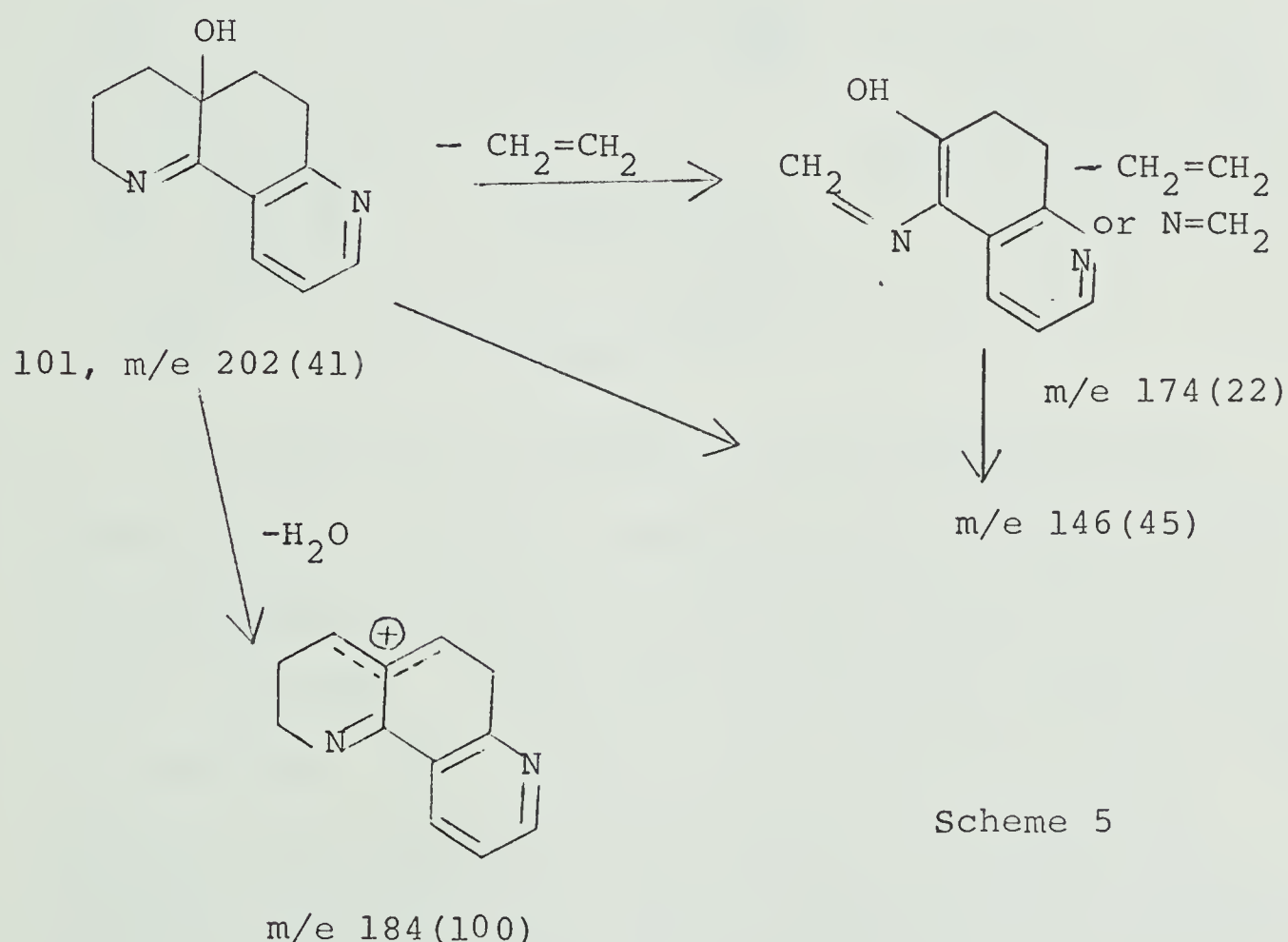
Therefore, instead of attempting to form the ethylene ketal, the cyano enamine 99 was reduced directly with lithium aluminum hydride <sup>55</sup> in tetrahydrofuran. Subsequent hydrolysis of the amino enamine 100 gave, instead of the expected imine 98, a hydroxy imine 101.



Since at this point the structure of the hydroxy imine 101 had not been ascertained a different route was investigated. Parcell <sup>56</sup> had reported that 3-bromopropylamine hydrobromide reacts with suitable enamines in dimethylformamide to form a tetrahydropyridine ring. The 3-bromopropylamine hydrobromide <sup>57a</sup> was conveniently prepared by heating 3-aminopropan-1-ol in constant boiling hydrobromic acid. The enamine 96 was stirred with a one and a half molar equivalents of 3-bromo-propylamine hydrobromide in dry dimethylformamide for one day. The semi-crystalline product was recrystallised from ethyl acetate to give in good yield the same hydroxy imine 101 as obtained before.



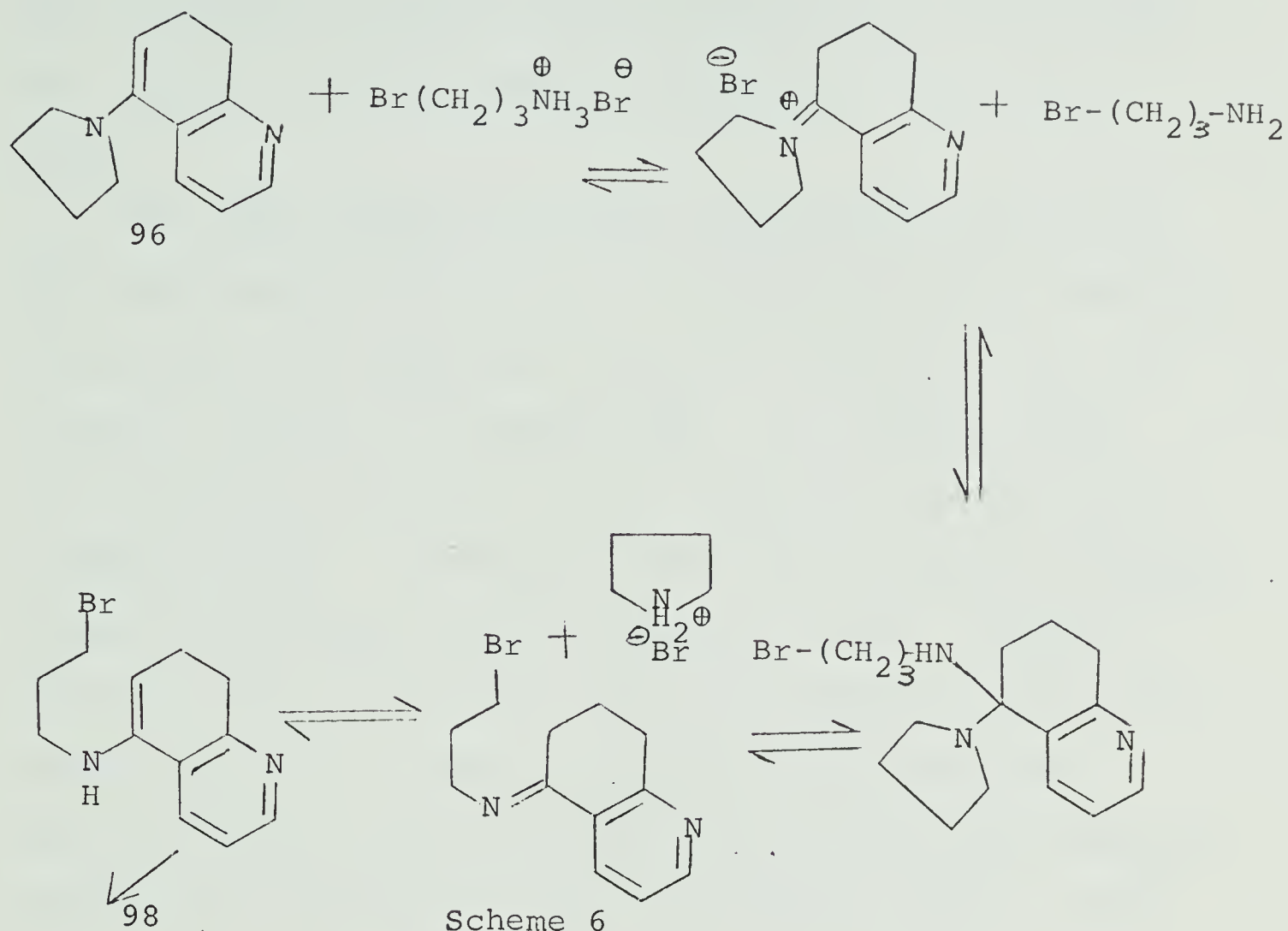
The ultraviolet spectrum of the product showed maxima at 235 and 280 mμ. The infrared spectrum had absorptions at 1630  $\text{cm}^{-1}$  and 3600  $\text{cm}^{-1}$  attributed to an imino and hydroxyl group respectively. The nmr spectrum gave no clue as to the structure except for the usual pyridine absorptions. The analysis calculated for  $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}$  which was confirmed by the mass spectrum which showed a molecular ion at 202. The mass spectral fragmentation is shown in scheme 5.



The mechanism for this ring addition has been presented by Parcell as shown in scheme 6.





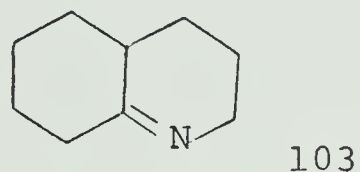
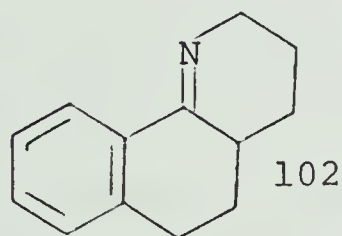


The imine 98 is probably an intermediate to the hydroxy imine. When the reaction with 3-bromopropylamine hydrobromide was repeated using much less dimethylformamide as solvent, a crystalline precipitate formed during the reaction. The crystals were filtered to give a 70% yield of the imine 98. The structure was proven by analysis ( $C_{12}H_{14}N_2$ ) and the mass spectrum which showed a parent peak at the molecular weight (186). The only readily interpretable fragment was at M-28 (158) caused by retro Diels Alder fragmentation (loss of ethylene).



The ultraviolet spectrum showed absorption at 241 and 287 mμ, and the infrared spectrum at 1655 cm<sup>-1</sup> due to the imine.

The imine 98 when stirred in chloroform for one day gave pure hydroxy imine 101. No hydroperoxide was detected. Parallels of this reaction have been reported in the literature. Parcell<sup>56</sup> reported that the tricyclic imine 102 underwent spontaneous aerial oxidation to the corresponding alcohol. He suggests that the intermediate peroxide is able to oxidise another molecule of imine. Witkop<sup>55</sup> reported that the bicyclic imine 103 underwent spontaneous aerial oxidation to give a crystalline hydroperoxide, which in solvents such as chloroform and methylene chloride react with the solvent to give the hydroxy imine. It is

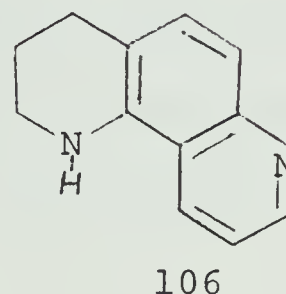
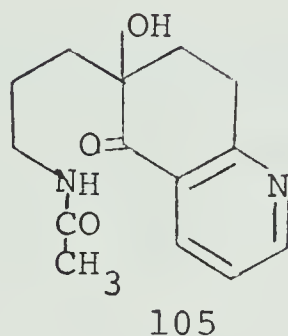
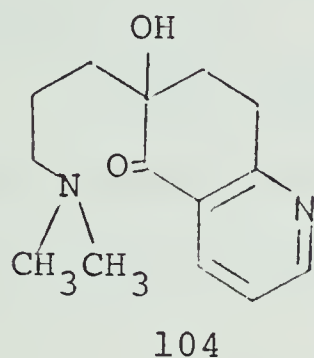


therefore presumed that the imine 98 is oxidised by the oxygen in the air to the hydroperoxide which very rapidly is converted to the hydroxy imine 101.

In order to obtain further proof for the structure of the hydroxy imine it was methylated by the Eschweiler-



Clarke procedure. The product was not fully characterised but the nmr spectrum showed a six proton singlet at  $\tau$  7.82 for a N,N-dimethyl group, and the infrared spectrum showed hydroxyl absorption at  $3600\text{ cm}^{-1}$ , a ketone at  $1690\text{ cm}^{-1}$ , and N-methyl at  $2790\text{ cm}^{-1}$ . The structure assigned is 104.

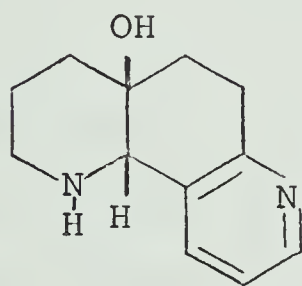


Acetylation with acetic anhydride and pyridine gave an impure product, which showed ketone absorption at  $1700\text{ cm}^{-1}$ , hydroxyl at  $3600\text{ cm}^{-1}$ , and secondary amide bands in the infrared spectrum, indicating structure 105. Dehydration with phosphorus oxychloride gave the quinoline 106. Evidence for this structure came from the ultra-violet spectrum with absorption at 262, 302, 308 and 343  $\mu$  which are similar to reported values for 5-amino quinoline.<sup>58</sup> The infrared spectrum showed absorption at 1482, 1575, 1585,  $3020\text{ cm}^{-1}$  which is consistent with reported values for quinolines,<sup>53</sup> and N-H absorption at  $3440\text{ cm}^{-1}$ . The nmr spectrum showed a two proton multiplet at  $\tau$  8.0 for methylene, a two proton multiplet at  $\tau$  7.07

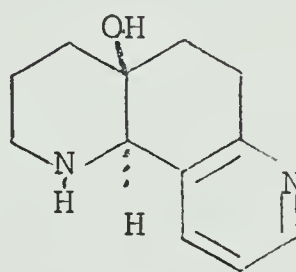


for a methylene adjacent to an aromatic ring, a two hydrogen multiplet at  $\tau$  6.60 for a methylene adjacent to an amine, a three hydrogen multiplet at  $\tau$  2.6 - 2.9 for benzene hydrogens and the pyridine  $\beta$  hydrogen. The pyridine  $\alpha$  and  $\gamma$  hydrogens showed one proton quartets at  $\tau$  0.96 and  $\tau$  1.90 respectively.

Sodium borohydride reduction of the hydroxy imine 101 gave two products which were shown to be the corresponding secondary amines 107 and 108. Some of the major product

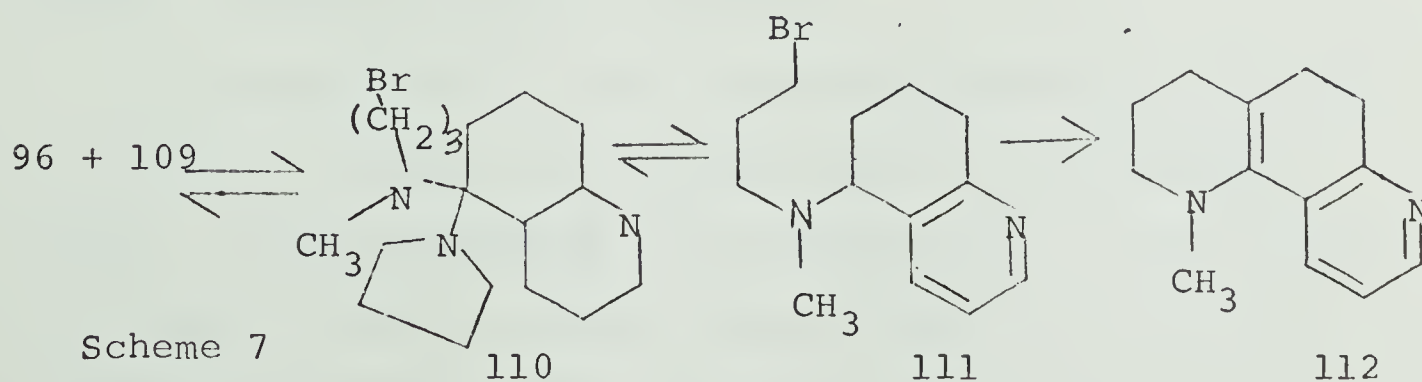


107



108

was separated by crystallisation. The remainder was acetylated and the two N-acetyl compounds were separated by column chromatography.

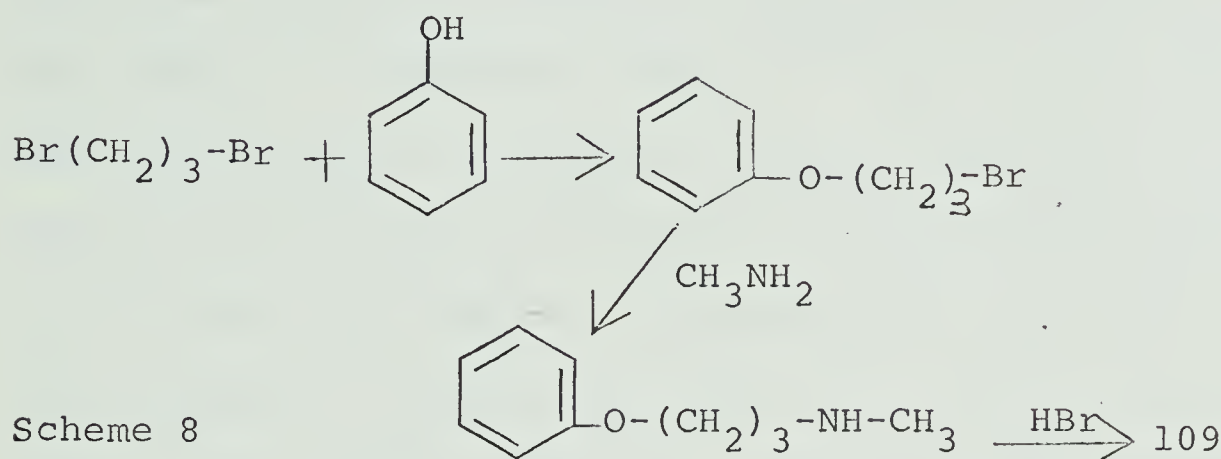






Parcell <sup>56</sup> also reported that 1-bromo-3-N-methyl-aminopropane hydrobromide (109) could be added to enamines as shown in scheme 7.

The hydrobromide 109 was prepared as shown in scheme 8.



Scheme 8

The reaction was attempted under varying conditions but only starting ketone 93 was obtained, and no enamine 112. The reason for the failure is probably due to the steric hindrance in intermediates such as 110 and 111, forcing the equilibrium to the left.

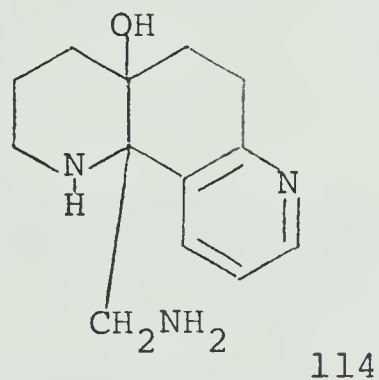
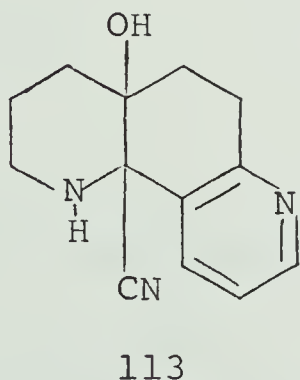
The possibility that the side chain could be added by Grignard addition to the imines 98 or 101 was tested with methylmagnesium iodide. The addition either gave back starting material with no reaction or gave decomposition to several uncharacterisable products.

An attempt to form the quaternary immonium salt 90 was made by treating the hydroxy imine 101 with methyl iodide. A mono-methiodide was crystallised in good yield, but infrared and nmr spectral data showed it to be the pyridine methiodide. The structure was confirmed by



reduction of the methiodide with sodium borohydride to a product which showed no pyridine absorption in the ultra-violet spectrum.

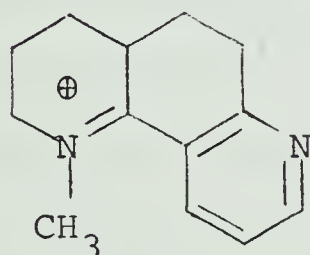
As steric hindrance seemed to be a problem and since the imine showed no tendency to go into the enamine form the addition of hydrogen cyanide <sup>59</sup> was investigated. Hydrogen cyanide was bubbled through a solution of the hydroxy imine 101 in chloroform giving a quantitative yield of the amino nitrile 113. Unfortunately this amino nitrile was extremely unstable, and under most conditions reverted back to the hydroxy imine 101. Reaction with pyridine-acetic anhydride, formic acid-formaldehyde, methyl magnesium iodide or phosphorus oxychloride all gave the same products as were obtained directly from the hydroxy imine 101. Lithium aluminum hydride reduction however gave a product which was homogeneous on tlc and appeared to be the tri-amine 114.



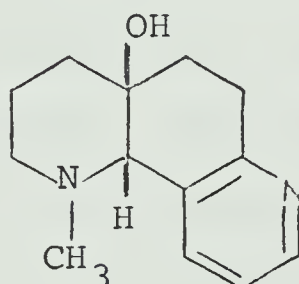


Reaction of the triamine with nitrosyl chloride, intended to replace the amino group with a chloro group, gave intractable material. Diazotisation of the triamine, intended to replace the amino group with a hydroxyl group, also gave intractable material. This route was then abandoned.

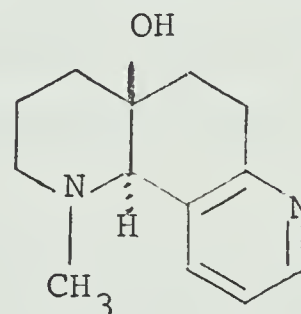
Other methods for forming the enamine 112 or the immonium salt 115 were sought. The hydroxy amines 107 and 108, and the major hydroxy amine (either 107 or 108, as there is no way of differentiating between them) were methylated separately using formic acid-formaldehyde to give the hydroxy N-methyl-amines 116 and 117. The major



115



116



117

amine gave one product, whereas the mixture gave two products (by tlc).

Dehydration of the hydroxy N-methylamines 116 and 117 with constant boiling hydrobromic acid gave an impure salt which could not be crystallised. Ultraviolet and



nmr spectra indicated that a mixture of products had been obtained. Basification gave a mixture of three components as indicated by tlc. The infrared spectrum showed absorption at  $1630\text{ cm}^{-1}$ , indicating an enamine. Rapid decomposition of the product prevented purification.

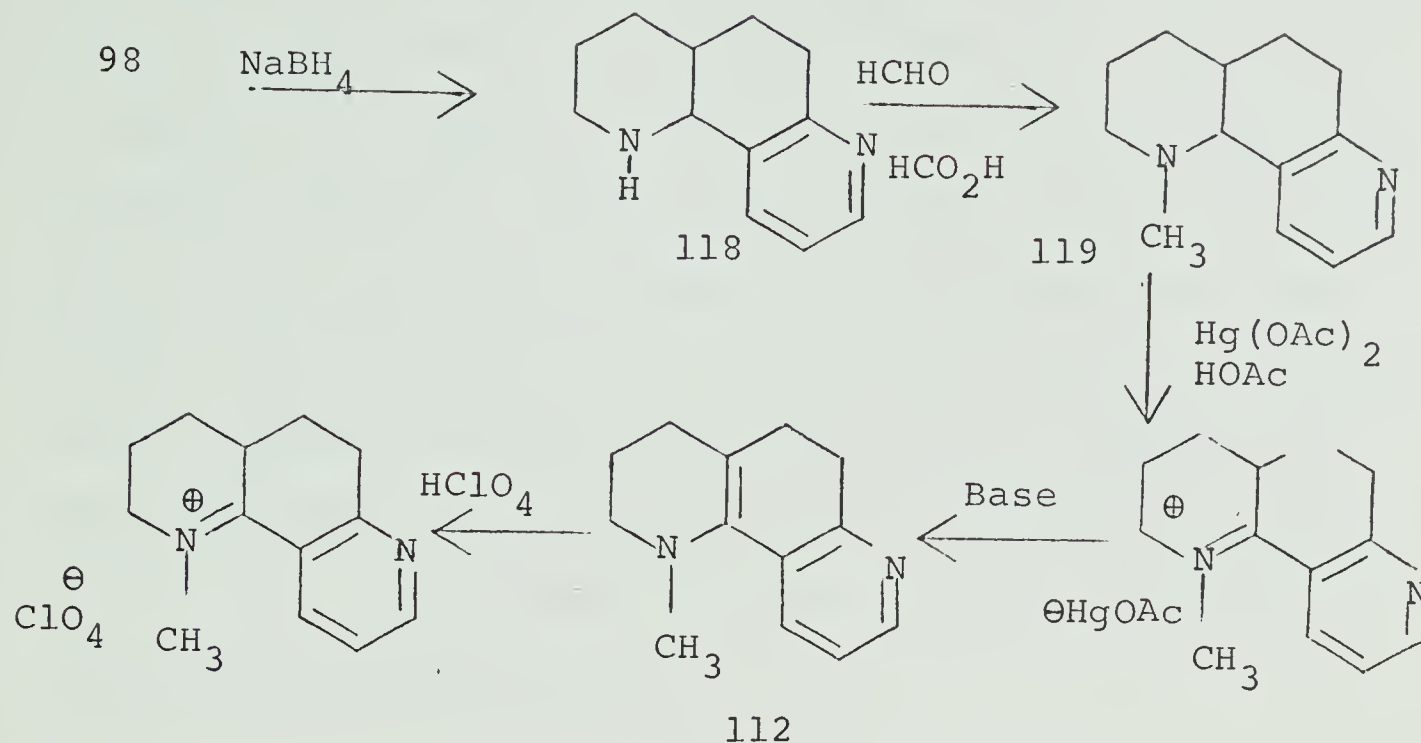
Dehydration was also attempted using phosphorus oxychloride. The basic product was shown to be mainly one component with several minor impurities (by tlc). The infrared spectrum showed no hydroxyl absorption, and enamine absorption at  $1630\text{ cm}^{-1}$ . Acidification with perchloric acid did not however give a crystalline immonium salt. The tlc and infrared spectra of products from the major isomer, and from the mixture, were identical, indicating loss of stereochemical difference, which would occur if the enamine 112 were formed. Rapid decomposition again prevented purification of the product.

One of the problems encountered was the instability of the enamine. If the enamine could be produced in a pure form, it was felt that it might be possible to transform it immediately to a stable, crystalline salt. Mercuric acetate oxidation<sup>60</sup> was attempted as outlined in scheme 9.

The imine 98 was reduced with sodium borohydride to the amine 118. Tlc indicated the presence of only one isomer, unless the  $R_F$  values of the two possible stereo-

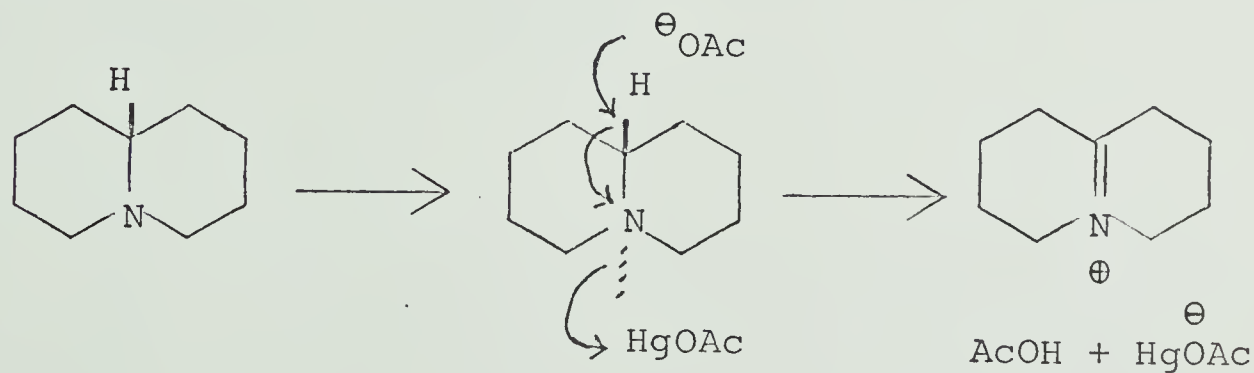






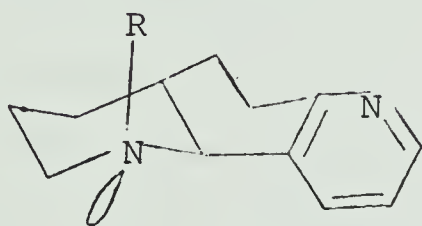
Scheme 9

isomers are identical. The amine 118 was methylated to the N-methylamine 119, which again showed only one spot on tlc. Mercuric acetate oxidation gave back pure starting material. Mercuric acetate oxidation of amines proceeds most readily when there is a trans-diaxial relationship between the nitrogen lone pair and an  $\alpha$ -hydrogen.



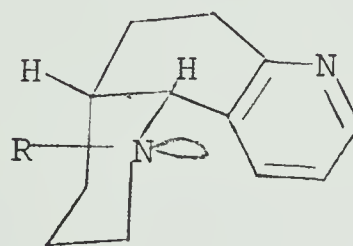


This relationship also gives rise to Bohlmann bands <sup>46</sup> in the infrared spectrum. Bohlmann <sup>61</sup> has also shown that compounds not showing these bands do not undergo mercuric acetate oxidation. These bands are not present in either the N-methylamine 119 or the amine 118 indicating that these compounds have the nitrogen free electrons equatorial and the hydrogen and methyl groups axial. Sodium borohydride reduction of the imine 98 must then give either 120 or 121. The N-methyl amine is therefore 122 or 123 (favoured conformations).



120, R=H

122, R=CH<sub>3</sub>



121, R=H

123, R=CH<sub>3</sub>

This work was abandoned at this stage to continue the synthesis of lycopodine.



## Experimental

### Part 2

Nuclear magnetic resonance spectra (nmr) were measured on a Varian Associates Model A-60 spectrometer or a Varian Associates Model HR-100 spectrometer with tetramethylsilane as an internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 421 dual grating infrared spectrometer or a Perkin-Elmer Model 337 grating infrared spectrometer. Mass spectra were determined on an A.E.I. Model MS-2H or an A.E.I. Model MS-9 mass spectrometer. Melting points were determined on a Fisher-Johns or a Leitz Wetzlar melting point apparatus and are uncorrected. Alumina, unless otherwise specified, means BDH basic alumina of activity III-IV (Brockman scale). Tlc was carried out using Research Specialty Company aluminum oxide G or E. Merck aluminum oxide H. Ultraviolet (uv) spectra were measured on a Cary Model 14 Recording spectrometer with 1 cm. quartz cells.

#### The Attempted Synthesis of Lycodine.

##### 1,3-Cyclohexadione.

Resorcinol (275 gms, 2.5 moles), sodium hydroxide (120 gms), and Raney nickel <sup>52b</sup> (W-2, 50 gms) were added to water (500 ml). The suspension was hydrogenated at 1110 psi and 50° for 12 hours. The bomb was then cooled



and the solution removed and acidified with conc. hydrochloric acid. The solution was left in the fridge for 48 hours and then filtered to give white crystals (60 gms, 21%): mp 100-102° (reported 103-104°).<sup>52a</sup> Commercial material (Aldrich Chemical Co.) was used in later experiments.

#### 1-Aminocyclohex-1-en-3-one

1,3-Cyclohexadione (140 gms, 1.25 moles) was dissolved in benzene (1ℓ) in a flask fitted with a Dean-Starke water separator. The solution was refluxed and ammonia was bubbled through the solution until the theoretical amount of water had separated. The solution was cooled and the benzene decanted, leaving a red gum. The gum was crystallised three times from acetone to give yellow crystals (71 gms, 0.64 moles, 51%): mp 128-129° (reported 128-131°)<sup>51a</sup>; uv max (95% ethanol) 283 mμ; ir (nujol) 1670 cm<sup>-1</sup> (C=O), 3140, 3320 cm<sup>-1</sup> (NH<sub>2</sub>); nmr (D<sub>2</sub>O) τ 7.5-8.3 (6H, CH<sub>2</sub>), 4.78 (1H, s, C=CH).

#### 7,8-dihydro-5(6H)-quinolone

1-Aminocyclohex-1-en-3-one (47 gms, 0.43 moles) was dissolved in dimethylformamide (125 ml). Propynal<sup>51b</sup> (23 gms, 0.43 moles) was added to the solution with stirring. After the exothermic reaction had subsided the solution was heated at 100° for one hour. The volatile component was distilled from the reaction at 130° (35 mm). The black residue was dissolved in 1N hydrochloric acid





(200 ml), extracted with chloroform (50 ml, five times), basified with sodium hydroxide, and extracted with ether (75 ml, four times). The ethereal extract was dried ( $\text{MgSO}_4$ ), and evaporated to an oil. This oil and the distillate from above were combined and distilled at  $80-82^\circ$  (1 mm) to give a colourless liquid (34.4 gms, 0.23 moles, 56%); uv max (95% ethanol) 233, 278 m $\mu$  ( $\epsilon = 4000$ ); ir ( $\text{CCl}_4$ ) 700, 900, 1120, 1560, 1570, 3070  $\text{cm}^{-1}$  (pyridine), 1685  $\text{cm}^{-1}$  (C=O); nmr ( $\text{CDCl}_3$ )  $\tau$  6.8-7.9 (6H,  $\text{CH}_2$ ), 2.72 (1H, q, pyridine  $\beta$ H), 1.75 (1H, q, pyridine  $\gamma$ H), ( $J_{\alpha\beta}=5$  cps,  $J_{\alpha\gamma}=2$  cps,  $J_{\beta\gamma}=8$  cps); mass spectrum ( $200^\circ$ , heated inlet) m/e (rel. intensity) 147(68), 119(100), 91(57).

#### 5-Pyrrolidino-7,8-dihydroquinoline

7,8-dihydro-5(6H)-quinolone (8.69 gms, 59 mmols) and pyrrolidine (11.72 gms, 165 mmols) were refluxed in dry toluene under a Dean-Starke water separator. The apparatus had been flame dried. The reaction was carried out under anhydrous conditions under nitrogen. p-Toluene-sulphonic acid (50 mg) was added to the solution. The reaction was halted when the theoretical amount of water had separated (about two days). The toluene was evaporated and the residual liquid distilled at  $135-140^\circ$  (1 mm) to yield a clear liquid (7.0 gms, 35 mmols, 60%); ir ( $\text{CCl}_4$ )



1550-1570,  $3060\text{ cm}^{-1}$  (pyridine),  $1620\text{ cm}^{-1}$  (enamine); nmr ( $\text{CDCl}_3$ )  $\tau$  7.0-8.3 ( $\text{CH}_2$ ), 4.8 (t,  $J=4$  cps,  $\text{C}=\text{CH}$ ), 2.9, 2.4, 1.7 (pyridine H).

The experiment was attempted using benzene as solvent and in toluene without p-toluenesulphonic acid. In both cases very low yields were obtained.

6-(2-Cyanoethyl)-7,8-dihydro-5(6H)-quinolone

The crude undistilled 5-pyrrolidino-7,8-dihydroquinoline (from 5 gms of 7,8-dihydro-5(6H)-quinolone) and acrylonitrile (3.0 gms, 1.5 molar equiv., freshly distilled) were refluxed in absolute ethanol (100 ml) for 12 hours under nitrogen. Water (10 ml) was added and the refluxing was continued for six hours. On cooling, crystals appeared which were filtered. (3.7 gms). The filtrate was concentrated to yield oily crystals. Tlc showed a mixture of product and 7,8-dihydro-5(6H)-quinolone. The mixture was separated by column chromatography on alumina. Elution with Skellysolve B (1 $\ell$ ) gave pure 7,8-dihydro-5(6H)-quinolone (1.0 gm, 20%). Elution with 5% benzene: Skellysolve B (100 ml) gave a mixture (0.4 gms). Elution with benzene (800 ml) gave the product (1.3 gms). All the crystalline material was recrystallised from n-hexane to give pure white crystals (4.7 gms, 66%): mp 92-93°; ir (nujol) 1572, 1582,  $3060\text{ cm}^{-1}$  (pyridine),  $1682\text{ cm}^{-1}$  ( $\text{C}=\text{O}$ ),  $2750\text{ cm}^{-1}$  ( $\text{C}\equiv\text{N}$ ): nmr ( $\text{CDCl}_3$ )  $\tau$  6.6-8.0 (9H,  $\text{CH}_2$  and CH), 2.70, 1.74,



1.27 (3H, 3q, pyridine H); mass spectrum (200°, heated inlet) m/e (rel. intensity) 200(4), 172(41), 147(100), 119(90), 91(49): Anal. Calcd for  $C_{12}H_{12}N_2O$ : C, 71.97; H, 6.04; N, 13.99. Found: C, 71.87; H, 6.28; N, 14.02.

Attempted Ethylene Ketal Formation with 6-(2-Cyanoethyl)-7,8-dihydro-5(6H)-quinolone.

Method 1 6-(2-Cyanoethyl)-7,8-dihydro-5(6H)-quinolone (1.0 gm, 5 mmoles), ethylene glycol (1.3 gms, 21 mmoles) and p-toluenesulphonic acid (1.8 gms, 9.4 mmoles) were refluxed in toluene (60 ml) with a Dean-Starke water separator for 26 hours.. No water separated from the reaction. Water was added (250 ml) and the solution basified with sodium bicarbonate. The solution was extracted with chloroform (100 ml, three times), dried ( $MgSO_4$ ) and evaporated to a black oil (0.9 gms). Tlc indicated mainly starting material and some polar components. On separation by column chromatography the other components were not the ketal and could not be characterised. Similar results were obtained using benzene as the solvent.

Method 2 6-(2-Cyanoethyl)-7,8-dihydro-5(6H)-quinolone. (0.95 gms , 4.8 mmoles) was added to ethylene glycol (40 ml). Boron trifluoride etherate (1.5 ml, freshly distilled) was added and the solution stirred for 30 hours. Water was added (250 ml) and the resulting aqueous solution extracted



with chloroform (75 ml, four times). On drying ( $\text{MgSO}_4$ ) and evaporation, starting material (0.8 gm) was obtained (by ir and tlc).

More vigorous conditions were used (stirred and heated at  $100^\circ$  for three days) but yielded starting material as well as intractable material.

#### The Hydroxy Imine 101 (Method 1)

The enamine from 7,8-dihydro-5(6H)-quinolone (5 gms, 34 mmoles) was reacted as before with acrylonitrile. The enamine was not hydrolysed. The ethanol was removed by evaporation and the residue dissolved in dry tetrahydrofuran (250 ml). Lithium aluminum hydride (5 gms) was added over 40 minutes at such a rate that the reaction did not become too vigorous. The reaction mixture was then refluxed for 24 hours. Water (5 ml) then 15% sodium hydroxide solution (5 ml), and then water (5 ml) were added dropwise and the resulting precipitate filtered off. Most of the solvent was evaporated and the residue taken up in water (20 ml) and 2N sodium hydroxide solution (5 ml), and heated on a steam bath for four hours. Water (100 ml) was added and the solution extracted with chloroform (75 ml, five times), dried ( $\text{MgSO}_4$ ), and evaporated to a gum (3.5 gms). Tlc showed one main component. The gum was purified by column chromatography. Elution with benzene (2l) gave non-polar material. Elution with ether (1500 ml) gave the





crystalline hydroxy imine 101 (1.0 gm). Elution with chloroform gave unidentifiable material.

The hydroxy imine 101 was recrystallised from ethyl acetate to give white crystals: mp 196-197°; uv max (95% ethanol) 235, 280 mμ; ir (CHCl<sub>3</sub>) 1570, 1580, 3060 cm<sup>-1</sup> (pyridine), 1630 (C=N), 3600 cm<sup>-1</sup> (OH); nmr (deuterio-dimethylsulphoxide) τ 7.9-8.3 (6H, CH<sub>2</sub>), 6.9 (2H, m, CH<sub>2</sub> adjacent to pyridine ring), 6.2 (2H, m, C=N-CH<sub>2</sub>), 2.6, 1.62, 1.36 (3H, 3q, pyridine H); mass spectrum (200°, heated inlet) m/e (rel. intensity) 202(41), 184(100), 174(22), 146(45), 131(80), 118(50); Anal. Calcd for C<sub>12</sub>H<sub>14</sub>N<sub>2</sub>O: C, 71.30; H, 6.98; N, 13.81. Found: C, 71.25; H, 6.96; N, 13.65.

### 3-Bromopropylamine Hydrobromide.

3-Amino-1-propanol (50 gms, 0.66 moles) was added dropwise to conc. hydrobromic acid at 0° over one hour with vigorous stirring. The water formed was slowly distilled off over 20 hours. The reaction mixture was poured into acetone (180 ml). After cooling at 0° for 12 hours the crystals were filtered off and washed with acetone. Recrystallisation from acetone gave pure white crystals (130 gms, 0.59 moles, 90%); mp 166-168° <sup>57a</sup>; nmr (D<sub>2</sub>O) τ 7.6 (2H, m, CH<sub>2</sub>), 6.67 (2H, t, J=6.5 cps, CH<sub>2</sub>Br), 6.30 (2H, t, J=6.5 cps, CH<sub>2</sub>-N).



### The Hydroxy Imine 101 (Method 2)

5-Pyrrolidino-7,8-dihydroquinoline (2.5 gms, 12.5 mmoles) and 3-bromopropylamine hydrobromide (4.0 gms, 18 mmoles) were stirred in dry dimethylformamide (75 ml, distilled from barium carbonate) for one day. The colour slowly went red. The reaction was poured into water (100 ml) and basified with sodium hydroxide. The solution was extracted with chloroform (75 ml, five times), dried ( $\text{MgSO}_4$ ), and evaporated to yield gummy crystals. The crystals were washed with ether and recrystallised from ethyl acetate (1.75 gms, 8.7 mmoles, 70%). The ir and tlc were identical to the previous product. The reaction was also attempted in refluxing dimethylformamide but considerably lower yields (15%) were obtained.

### N-Methylation of the Hydroxy Imine 101

The hydroxy imine 101 (600 mg) was refluxed in 40% formaldehyde (3 ml) and 98% formic acid (3 ml) for two days. The reaction was diluted with water (50 ml) and basified with sodium hydroxide. The solution was extracted with chloroform (50 ml, five times), dried ( $\text{MgSO}_4$ ), and evaporated. The product was purified by column chromatography on alumina. Elution with chloroform (50 ml) gave two components with almost identical  $R_F$  values (420 mg): non-crystalline; ir ( $\text{CHCl}_3$ )  $1670, 1680 \text{ cm}^{-1}$  (pyridine),



1690  $\text{cm}^{-1}$  (C=O), 2790, 2870  $\text{cm}^{-1}$  (NMe), 3600  $\text{cm}^{-1}$  (OH);  
nmr ( $\text{CDCl}_3$ )  $\tau$  8.0-8.4 (6H,  $\text{CH}_2$ ), 7.82 (8H, strong s and  
weak m, N- $\text{CH}_3$ ,  $\text{CH}_2$ -N), 6.75 (2H, t,  $\text{CH}_2$  adjacent to pyri-  
dine ring), 2.60, 1.60, 1.20 (3H, 3q, pyridine H). Spectra  
indicate the structure to be 6-(3-N,N dimethylaminopropyl)-  
6-hydroxy-7,8-dihydro-5(6H)-quinolone. Similar treatment  
of the imine 98 gave the same product and the hydroxy  
imine 101.

#### Acetylation of the Hydroxy Imine 101

The hydroxy imine 101 (400 mg) was stirred in acetic  
anhydride (20 ml) and pyridine (10 ml) for two days.  
The reaction mixture was basified with conc. ammonium  
hydroxide and extracted with chloroform (50 ml, five times),  
dried ( $\text{MgSO}_4$ ), and evaporated to a gum (450 mg). Tlc  
indicated two main components and several minor ones. An  
attempt was made at separation by column chromatography.  
Although not obtained pure the major components showed  
secondary amide absorption - 1510, 1670, 3200, 3350, 3410,  
3450, 3500, 3530  $\text{cm}^{-1}$ , ketone-1700  $\text{cm}^{-1}$  and hydroxyl-3600  
 $\text{cm}^{-1}$ , indicating a ring opened product.

#### Dehydration of the Hydroxy Imine 101

The hydroxy imine 101 (200 mg, 1 mmole) was refluxed  
in pyridine (5 ml) and phosphorus oxychloride for seven  
hours under anhydrous conditions. Excess phosphorus oxy-



chloride was destroyed with methanol and water was added (100 ml). The solution was basified with conc. ammonium hydroxide and extracted with chloroform (50 ml, five times), dried ( $\text{MgSO}_4$ ), and evaporated. Tlc indicated some starting material and a less polar compound. The components were separated by column chromatography. Elution with chloroform (50 ml) gave the product (110 mg, 0.6 mmoles, 60%): semi-crystalline; uv max (85% ethanol) 262 m $\mu$  (strong) 302, 308, 343 m $\mu$  (weak) and with addition of 0.1 N HCl; 257 m $\mu$ , 283 (strong), 308, 351 m $\mu$ ; ir ( $\text{CHCl}_3$ ) 1482, 1575, 1585, 3020  $\text{cm}^{-1}$  (quinoline), 3440  $\text{cm}^{-1}$  (NH); nmr ( $\text{CDCl}_3$ )  $\tau$  8.0 (2H,  $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 7.07 (2H,  $\text{CH}_2$  adjacent to aromatic ring) 6.60 (2H,  $\text{CH}_2\text{-N}$ ), 5.53 (1H, broad, NH), 2.6-2.9 (3H, m, pyridine  $\beta$ , and benzene H), 1.90 (1H, q, pyridine  $\gamma$ H), 0.96 (1H, q, pyridine  $\alpha$ H).

The dehydration was also attempted in boiling conc. hydrochloric acid and with p-toluenesulphonic acid in benzene. Both reactions gave back starting material.

#### The Hydroxy Amines 107 and 108.

The hydroxy imine 101 (430 mg, 2.13 mmoles) was dissolved in methanol (20 ml). Sodium borohydride (554 mg, 14.5 mmoles) was added portionwise (at such a rate that the reaction did not become too vigorous) with stirring. The stirring was continued for four hours. The solvent was





evaporated and the residue dissolved in water (25 ml). The solution was basified with sodium hydroxide and stirred for an additional two hours. Extraction with chloroform (50 ml, five times), drying ( $\text{MgSO}_4$ ), and evaporation led to a yellow gum (380 mg). Tlc showed two components, one with the same  $R_F$  value as the starting material, however, the ir showed no  $\text{C}=\text{N}$  absorption at  $1630\text{ cm}^{-1}$ . The gum was dissolved in ether and allowed to cool. Crystals appeared which tlc showed to be the major, less polar, component. Concentration of the ether led to more crystals (total 230 mg). The gum left on evaporation of the ether (146 mg) consisted of about 70% of the more polar minor component.

Major component (approx. 65%): mp  $167-168^\circ$ ; uv max (95% ethanol)  $267\text{ m}\mu$ ; ir ( $\text{CHCl}_3$ )  $1575, 1585\text{ cm}^{-1}$  (pyridine),  $3600\text{ cm}^{-1}$  (OH); (nujol)  $1565, 1575\text{ cm}^{-1}$  (pyridine),  $3200\text{ cm}^{-1}$  (broad, OH),  $3270, 3280\text{ cm}^{-1}$  (sharp, NH); nmr ( $\text{CDCl}_3$ )  $\tau$  6.42 (1H, s, N-CH-pyridine), 2.88, 2.26, 1.60 (3H, q, pyridine  $\beta, \gamma, \alpha, \text{H}$  resp.); mass spectrum ( $185^\circ$ , direct probe) m/e (rel. intensity) 204.1262 (100; calcd for  $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O} = 204.1263$ ), 187(14), 186(13), 185(14), 161(26), 147(35), 133(70). The mixture of the two components showed a similar uv spectrum, and the ir and nmr were similar but not identical.



The Imine 98

5-Pyrrolidino-7,8-dihydroquinoline (14 gms, 70 mmoles) and 3-bromopropylamine hydrobromide (17 gms, 78 mmoles) were stirred in dimethylformamide (50 ml, dried by distillation from barium carbonate) for one day. After about five hours the whole solution went solid with crystallisation. The crystals were filtered and washed with ethyl acetate to give pure white crystals (10 gms, 72%) which rapidly turned pink and then purple on exposure to the air. Further workup of the filtrate did not yield any hydroxy imine. The imine was recrystallised from ethyl acetate to give purple crystals, mp 199-201°; uv max (95% ethanol) 241, 287 mμ; shifting to 252, 284 mμ with the addition of 0.1N HCl; ir (CHCl<sub>3</sub>) 1570, 1590, 3020 cm<sup>-1</sup> (pyridine), 1655 cm<sup>-1</sup> (C=N), (nujol) same absorptions; nmr (CDCl<sub>3</sub>) τ 7.5-8.1 (6H, CH<sub>2</sub>), 6.8 (2H, CH<sub>2</sub> adjacent to pyridine), 5.9 (2H, C=N-CH<sub>2</sub>), 2.56, 1.17, 0.56 (3H, 3q, pyridine β, γ, α, H resp.); mass spectrum (175°, direct probe) m/e (rel. intensity) 186.1158 (100; calcd for C<sub>12</sub>H<sub>14</sub>N<sub>2</sub> = 186.1157), 185(40), 158(45), 157(30), 130(35).

Conversion of the Imine 98 to the Hydroxy Imine 101.

The imine 98 (3.10 gms, 16.7 mmoles) was stirred in chloroform (100 ml). Tlc of the solution after five minutes showed about 20% conversion, after five hours about 50%, and after thirty hours complete conversion.



The solvent was removed and the crystals recrystallised from ethyl acetate (3.0 gms, 14.9 mmoles, 90%). The structure was confirmed by ir, tlc and mp.

Acetylation of the Hydroxy Amines 107 and 108.

A mixture of the hydroxy amines 107 and 108 (40 mg) were stirred in dry pyridine (5 ml) and acetic anhydride (10 ml) for two days. Water (20 ml) was added and the solution basified with conc. ammonium hydroxide, dried ( $\text{MgSO}_4$ ), and evaporated to an oily residue. The tlc indicated two components which were separated by column chromatography on alumina. Elution with chloroform (50 ml) gave the major, less polar acetate (22 mg): ir ( $\text{CHCl}_3$ ) 1675, 1690  $\text{cm}^{-1}$  (pyridine), 1635, 3440  $\text{cm}^{-1}$  (N-acetate); mass spectrum (200°, heated inlet) m/e (rel. intensity) 246(1), 228(66), 203(25), 186(100), 185(77).

Further elution (50 ml) gave a mixture and then (100 ml) the pure minor acetate (11 mg): ir ( $\text{CHCl}_3$ ) 1675  $\text{cm}^{-1}$  (pyridine), 1630, 3410  $\text{cm}^{-1}$  (N-acetate); mass spectrum (185°, direct probe) m/e (rel. intensity) 246.1370 (3; calcd for  $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_2$  = 246.1368), 229(13), 228(80), 209(19), 187(17), 186(100), 185(59), 158(14).

1-Bromo-3-phenoxypropane.<sup>52b</sup>

1,3-Dibromopropane (400 gms, 1.98 moles) and phenol (148 gms, 1.48 moles) were stirred in a flask, and sodium



hydroxide (60 gms) in 200 ml water; 1.5 moles) added dropwise over two hours. The solution was refluxed for another six hours. The organic layer was separated and distilled at 1 mm. Material boiling between 95° and 97° was taken (220 gms, 1.02 moles, 51%): ir ( $\text{CCl}_4$ ) 695, 1040, 1500, 1600, 3060, 3080  $\text{cm}^{-1}$  (aromatic); nmr ( $\text{CDCl}_3$ )  $\tau$  7.75 (2H, m,  $\text{CH}_2\text{-CH}_2\text{-CH}_2$ ), 6.45 (2H, t,  $\text{CH}_2\text{Br}$ ) 6.95 (2H, t,  $\text{CH}_2\text{O}$ ), 2.6-3.2 (5H, aromatic).

1-N-Methylamino-3-phenoxypropane.

Pure methylamine was obtained by heating a 30% methylamine solution through which was passed a stream of nitrogen. The vapour was passed through a drying tube and then the methylamine condensed in a trap cooled by dry-ice acetone. Pure methylamine (100 ml) and 1-bromo-3-phenoxypropane (20 gms, 0.09 moles) were stirred in 95% ethanol (500 ml) for four days. The solvent was evaporated to give white crystals. The crystals were dissolved in 25% sodium hydroxide solution (100 ml) and extracted with ether (100 ml, five times). The ethereal solution was extracted with 1N hydrochloric acid (100 ml, twice), basified and extracted with ether (100 ml, five times). After drying ( $\text{MgSO}_4$ ), and evaporation, distillation at 1mm gave a colourless liquid (14 gms, 0.85 moles, 95%): bp 173-177°; ir ( $\text{CCl}_4$ ) 690, 1040, 1490, 1595, 3040, 3060  $\text{cm}^{-1}$





(aromatic),  $2795\text{ cm}^{-1}$  ( $\text{NCH}_3$ ); nmr ( $\text{CDCl}_3$ )  $\tau$  8.95 (1H, s, NH), 8.0 (2H, m,  $\text{CH}_2\text{-CH}_2\text{-CH}_2$ ), 7.25 (2H, t,  $\text{CH}_2\text{N}$ ), 6.0 (2H, t,  $\text{CH}_2\text{O}$ ), 2.6-3.2 (5H, aromatic).

1-Bromo-3-N-methylaminopropane Hydrobromide.<sup>52c</sup>

1-N-Methylamino-3-phenoxypropane (18 gms, 0.11 moles) was dissolved in conc. hydrobromic acid (100 ml). The solution was slowly distilled over an hour until white vapors appeared. The liquid residue was poured into acetone (100 ml), and ether added slowly with stirring. As the ether was added crystals formed, which were filtered (22 gms, 0.94 moles, 87%): mp  $63\text{-}65^\circ$  (reported  $64\text{-}68^\circ$ ), ir ( $\text{CHCl}_3$ ) 770, 1580,  $2760\text{ cm}^{-1}$  ( $\text{NH}_2^+$ ); nmr ( $\text{D}_2\text{O}$ )  $\tau$  7.7 (2H, m,  $\text{CH}_2\text{-CH}_2\text{-CH}_2$ ), 7.2 (3H, s,  $\text{NCH}_3$ ), 6.72 (2H, t,  $\text{CH}_2\text{N}$ ), 6.48 (2H, t,  $\text{CH}_2\text{Br}$ ).

Reaction of 5-Pyrrolidino-7,8-dihydroquinoline with 1-Bromo-3-N-methylaminopropane Hydrobromide.

5-Pyrrolidino-7,8-dihydroquinoline (7.3 gms, 0.37 moles) and 1-bromo-3-N-methylaminopropane hydrobromide (10 gms, 0.43 moles) were stirred in dry dimethylformamide (30 ml) for three days. The solution was diluted with water (100 ml), basified with sodium hydroxide and extracted with chloroform (75 ml, five times). The chloroform solution was re-extracted to remove neutral material, then dried ( $\text{MgSO}_4$ ), and evaporated to a red gum (7.0 gms). Tlc



indicated about 80% of the 7,8-dihydro-5(6H)-quinolone and several other more polar components. They were separated by column chromatography. The quinolone was identified by tlc, ir and nmr (6.0 gms). The other components, isolated in very small quantities, were unidentifiable and not the desired product.

The reaction was repeated and the product isolated directly from the reaction without basification, but it was still only the quinolone. The reaction was also repeated under reflux but with similar results.

Reaction of the Hydroxy Imine 101 and the Imine 98 with Methylmagnesium Iodide

The methylmagnesium iodide was prepared by refluxing magnesium and a 1.1 molar equivalent of methyl iodide in ether for twelve hours to prepare a stock solution.

The hydroxy imine 101 (403 mg, 2 mmoles) was refluxed with methylmagnesium iodide (4.5 mmoles from the stock solution) in ether (100 ml) under anhydrous conditions for four days. Material precipitated during the reaction. The solution was poured into water (100 ml) and extracted with chloroform (75 ml, five times), dried ( $\text{MgSO}_4$ ), and evaporated to give starting material (500 mg), shown by tlc and ir. Starting material was also obtained when tetrahydrofuran was used as the solvent.



The reaction was repeated using 'diglyme' (dried by distillation from lithium aluminum hydride) as solvent. After five days all the starting material had been consumed. Tlc showed six components in the product, none of which could be characterised.

The imine 98 was reacted in the same manner in tetrahydrofuran. After one day tlc indicated no reaction had occurred. After five days a product consisting of five components was obtained. None of the components could be characterised or isolated in major amounts. When repeated in 'diglyme' there was no reaction after one day and after four days most of the starting material had disappeared and been replaced by a number of components which could not be characterised.

#### The Hydroxy Imine 101 Methiodide

The hydroxy imine 101 (1.0 gms, 4.9 mmoles) and methyl iodide (7.1 gms, 5.6 mmoles) were refluxed in methanol (10 ml) for 24 hours. Crystals formed on cooling in the freezer. The crystals were filtered and recrystallised from methanol (700 ml). Tlc showed one component. The spectra showed the crystals to be pyridine monomethiodide: ir (nujol)  $1635\text{ cm}^{-1}$  (C=N); nmr ( $\text{D}_2\text{O}$ )  $\tau$  6.6 (2H, m,  $\text{CH}_2$  adjacent to pyridine), 6.1 (2H, broad, C=N- $\text{CH}_2$ ) 6.65 (3H, s,  $\text{NCH}_3$ ), 2.0 (1H, pyridine  $\beta\text{H}$ ), 1.0, 1.12 (2H, 2s, pyridine  $\alpha$  and  $\gamma\text{H}$ ).



Reduction with sodium borohydride gave a mixture of products which did not show pyridine or imine absorption in the ir. The ir did show  $\text{NCH}_3$  absorption at  $2800\text{ cm}^{-1}$ .

The Amino Nitrile 113.

Hydrogen cyanide was bubbled through a solution of the hydroxy imine 101 (1.04 gms, 5 mmoles) in ethanol free chloroform (300 ml, passed through a silica gel column to remove the ethanol). The hydrogen cyanide was prepared by dropping a solution of sodium cyanide (100 gms) in water (250 ml) into an excess of 70% sulphuric acid. The gas was dried by passing it in a stream of nitrogen through two calcium chloride drying tubes. The solution was allowed to stand for 24 hours and then the chloroform evaporated to give a white powder (1.15 gms, 5.1 moles, approx. quantitative yield): mp decomp; uv max (95% ethanol) 265, 272 m $\mu$ , with addition of 0.1 N HCl, 272 m $\mu$ ; ir (nujol)  $1580\text{ cm}^{-1}$  (pyridine),  $3160\text{ cm}^{-1}$  (broad, OH),  $3300\text{ cm}^{-1}$  (sharp, NH),  $2229\text{ cm}^{-1}$  ( $\text{C}\equiv\text{N}$ , very weak). Tlc showed one component, with an  $R_F$  different to that of starting material. The reaction was attempted using methanol as the solvent but without success.

The reaction was first attempted as follows. The hydroxy imine (272 mg) was added to water (20 ml) and acidified with perchloric acid. Potassium cyanide (1.65







gms, 20 molar excess) was added and the solution shaken with a mechanical shaker. After one day there was little reaction; after five days about 70% conversion. Further time did not increase the yield. The reaction was in each case worked up by basifying with 10% ammonium hydroxide solution and extracting with chloroform.

The compound was extremely unstable, reverting back to the hydroxy imine after one day of stirring in methanol, 1N hydrochloric acid or 10% ammonium hydroxide solution. When treated with pyridine-acetic anhydride, formic acid-formaldehyde, or phosphorus oxychloride as before, the products were identical to those obtained from the hydroxy imine 101. The hydroxy imine 101 was obtained when the cyano compound was refluxed in conc. hydrochloric acid for ten hours. Treatment with a five molar excess of methyl magnesium iodide in dry 'glyme' also gave the hydroxy imine 101 in good yield. Treatment with tosyl chloride in pyridine gave the same result.

#### The Triamine 114

The amino nitrile 113 (300 mg, 1.3 mmoles) was slowly added to a solution of lithium aluminum hydride (1.0 gm) in dry tetrahydrofuran (125 ml) with rapid stirring. The reaction mixture was refluxed for eight hours during which time the colour changed from green to red. The hydride



was decomposed by the dropwise addition of water (1 ml) and 15% sodium hydroxide solution (1 ml). The solution was filtered, dried ( $\text{MgSO}_4$ ), and evaporated to an oil (290 mg, 1.25 mmoles, 96%): non-crystalline; ir ( $\text{CHCl}_3$ ) 1575, 1585  $\text{cm}^{-1}$  (pyridine), 3100-3400  $\text{cm}^{-1}$  (broad with sharp peak at 3400  $\text{cm}^{-1}$ , NH and  $\text{NH}_2$ ), 3600  $\text{cm}^{-1}$  (OH); nmr ( $\text{CDCl}_3$ )  $\tau$  6.75 (2H, s, disappears on  $\text{D}_2\text{O}$  exchange,  $\text{NH}_2$ ), 6.3 (1H, broad, disappears on  $\text{D}_2\text{O}$  exchange, NH or OH), 2.80, 2.10, 1.50 (3H, q, pyridine  $\beta$ ,  $\gamma$ ,  $\alpha\text{H}$ ). Tlc showed only one component.

#### Treatment of the Triamine 114 with Nitrosyl Chloride.

The triamine 114 (270 mg) was dissolved in dry pyridine (50 ml). Nitrogen was passed through the solution to remove oxygen. Nitrosyl chloride was then bubbled through for two minutes. The pyridine was removed by evaporation and the residue dissolved in 1N hydrochloric acid (50 ml) and chloroform (100 ml). The water layer was separated and the organic layer extracted twice more with 1N hydrochloric acid (50 ml). The acidic solution was basified with sodium hydroxide, extracted with chloroform (50 ml, five times), dried ( $\text{MgSO}_4$ ), and evaporated to a black gum (140 mg). Tlc showed several products which could not be characterised.



Treatment of the Triamine 114 with Nitrous Acid.

The triamine 114 (240 mg) was dissolved in conc. hydrochloric acid (5 ml) and water (30 ml) and cooled to  $-5^{\circ}$ . Sodium nitrite solution (10%) was slowly added until starch-iodide paper gave a positive reaction. The solution was kept 30 minutes at  $-5^{\circ}$  and twelve hours at room temperature. The solution was then extracted with chloroform (50 ml), basified with sodium hydroxide, and extracted with chloroform (30 ml, five times). After drying ( $\text{MgSO}_4$ ) and evaporation a gum (150 mg) was obtained. Tlc indicated a variety of products.

The Hydroxy N-Methylamines 116 and 117

The hydroxy amine 107 or 108 (major component, 250 mg, 1.25 mmoles) was refluxed in 40% formaldehyde (6 ml) and formic acid (6 ml) for 12 hours. Most of the liquid was evaporated and the residue dissolved in water (50 ml). The aqueous solution was basified with sodium hydroxide, extracted with chloroform, dried ( $\text{MgSO}_4$ ), and evaporated to a semi-crystalline product (251 mg, 1.15 mmoles, 95%); ir ( $\text{CHCl}_3$ )  $1575, 1585, 3040 \text{ cm}^{-1}$  (pyridine),  $2800 \text{ cm}^{-1}$  ( $\text{NCH}_3$ ),  $3600 \text{ cm}^{-1}$  (OH); nmr ( $\text{CDCl}_3$ )  $\tau$  7.50 (3H, s,  $\text{NCH}_3$ ), 6.8-7.2 (4H,  $\text{CH}_2\text{N}, \text{CH}_2$  adjacent to pyridine ring), 6.36 (1H, s, N-CH-pyridine) 2.83, 2.13, 1.60 (3H, 3q, pyridine  $\beta, \gamma, \alpha\text{H}$ ); mass spectrum ( $185^{\circ}$ , direct probe) m/e (rel. intensity) 218.1418 (100; calcd for  $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O} = 218.1419$ )



201(12), 147(56), 133(34). Tlc showed only one component.

A mixture of both major and minor components from the sodium borohydride reduction was methylated under the same conditions. Tlc indicated two components with similar  $R_F$  values. The ir showed similar absorption but was not identical with the product from the major isomer.

Attempted Dehydration of the Hydroxy N-Methylamines 116 and 117.

A. Conc. Hydrobromic Acid. The hydroxy N-methylamine 116 or 117 (115 mg) was refluxed in conc. hydrobromic acid (7 ml) under nitrogen for three days. The acid was removed by evaporation. The residue was taken up in methanol and treated with Norite. A crystalline product could not be obtained; nmr ( $D_2O$ )  $\tau$  7.2 (s,  $NCH_3$ ), 1.85, 1.0, 0.8 (pyridine  $\beta$ ,  $\gamma$ ,  $\alpha H$ ), and uv max (95% ethanol) 223, 230, 276, 284, 317 m $\mu$  did not indicate a pure product. After basification with 10% ammonium hydroxide solution, extraction with ether (50 ml, three times), drying ( $MgSO_4$ ), and evaporation, a non-crystalline oil was obtained. Tlc indicated three components, ir ( $CHCl_3$ ) 1630  $cm^{-1}$  (enamine), but the components could not be separated due to rapid decomposition. Shorter reflux time led to incomplete reaction.





B. Phosphorus Oxychloride. The hydroxy N-methylamine 116 or 117 (97 mg) was refluxed in phosphorus oxychloride (7 ml) under nitrogen for three hours. Methanol was then added dropwise to decompose the excess phosphorus oxychloride. The reaction was basified with 10% ammonium hydroxide solution, extracted with ether (50 ml, three times), dried ( $\text{MgSO}_4$ ), and evaporated to a gum (60 mg): ir ( $\text{CHCl}_3$ ) 1560, 3050  $\text{cm}^{-1}$  (pyridine), 1630  $\text{cm}^{-1}$  (enamine), no hydroxyl absorption. Tlc showed one major component and several minor ones. Attempts at purification led to rapid decomposition. Acidification with perchloric acid: ethanol (1:1) did not yield a crystalline perchlorate. Both hydroxy N-methylamines 116 and 117 gave the same products (by tlc and ir). When the reaction was attempted using pyridine as a solvent no pure product was obtained. An attempt to crystallise the product without basification by evaporating the phosphorus oxychloride was also unsuccessful.

The Amine 118.

The imine 98 (1.55 gms, 8.3 mmols) was dissolved in methanol (50 ml) to which sodium borohydride (1.5 gms, 40 mmols) was added slowly. The solution was stirred for two hours, the methanol evaporated and the residue stirred



in water for one hour. The aqueous solution was extracted with chloroform (50 ml, five times), dried ( $\text{MgSO}_4$ ), and evaporated to an oil (963 mg, 5.1 mmoles, 61%): ir ( $\text{CCl}_4$ ) 1570, 1580, 3040, 3060  $\text{cm}^{-1}$  (pyridine); nmr ( $\text{CDCl}_3$ )  $\tau$  7.8-8.8 (7H, CH,  $\text{CH}_2$ ), 6.8-7.3 (5H,  $\text{CH}_2\text{N}$ ,  $\text{CH}_2$ -pyridine, N-CH-pyridine), 2.90, 2.08, 1.60 (3H, 3q, pyridine  $\beta$ ,  $\gamma$ ,  $\alpha$ H). Tlc showed only one component.

#### The N-Methylamine 119.

The amine 118 (963 mg, 5.1 mmoles) was refluxed in formic acid (10 ml) and 40% formaldehyde (10 ml) for twelve hours. The liquid was removed by evaporation and the residue dissolved in water (50 ml). The solution was basified with 10% sodium hydroxide solution and extracted with ether (50 ml, five times), dried ( $\text{MgSO}_4$ ), and evaporated to an oil. The oil was distilled at 1 mm at 170-175° to yield a colourless oil, which crystallised on standing (863 mg, 4.3 moles, 84%) uv max (95% ethanol) 268 m $\mu$ ; (0.1N HCl added) 270 m $\mu$ ; ir ( $\text{CCl}_4$ ) 1560, 3050, 3060  $\text{cm}^{-1}$  (pyridine), 2800  $\text{cm}^{-1}$  ( $\text{NCH}_3$ ); (nujol) 1570, 1580, 3040  $\text{cm}^{-1}$  (pyridine), 2800  $\text{cm}^{-1}$  ( $\text{NCH}_3$ ); nmr ( $\text{CDCl}_3$ )  $\tau$  7.9-8.8 (5H, CH,  $\text{CH}_2$ ), 7.83 (3H, s,  $\text{NCH}_3$ ), 6.8-7.2 (4H,  $\text{NCH}_2$ ,  $\text{CH}_2$ -pyridine), 6.30 (1H, d, N-CH-pyridine), 2.87, 2.12, 1.60 (3H, 3q, pyridine  $\beta$ ,  $\gamma$ ,  $\alpha$  H); mass spectrum (200° heated inlet) m/e (rel. intensity) 202(69),



201(54), 187(32), 163(12), 130(100), 110(69); mp, dihydroperchlorate 151-152° (with decomposition); ir (nujol) 1555, 1630  $\text{cm}^{-1}$  (pyridine), 3050-3250  $\text{cm}^{-1}$  ( $\text{NH}^{\oplus}$ ); Anal. calcd for  $\text{C}_{13}\text{H}_{18}\text{N}_2 \cdot 2\text{HClO}_4$ : C, 38.74; H, 5.00; N, 6.95. Found: C, 38.93; H, 4.78; N, 6.55.

Attempted Mercuric Acetate Oxidation of the N-Methylamine 119

The N-methylamine 119 (500 mg, 2.5 mmoles) and mercuric acetate (3.468 gms, 11 mmoles) were heated in 5% acetic acid (30 ml) on a steam bath for two hours. The mercurous acetate which formed was filtered off (1.71 gms, 66%). Hydrogen sulphide was bubbled through the solution and the mercuric sulphide filtered and washed with 5% acetic acid (50 ml). The aqueous solution was divided in two. One half was evaporated to dryness, taken up in acetone and acidified with perchloric acid; ethanol (1:1). On cooling white crystals were formed (2.40 mg), which had an ir spectrum identical with that of the N-methylamine 119 hydroperchlorate. The other half was basified with potassium carbonate, extracted with ether (50 ml, five times), dried ( $\text{MgSO}_4$ ) and evaporated to a gum (200 mg). The gum was immediately dissolved in acetone and acidified with perchloric acid: ethanol (1:1) to give crystals, again identical with the starting material hydroperchlorate (by ir). Basification and extraction with ether of both halves gave the N-methylamine 119 (by ir and tlc).



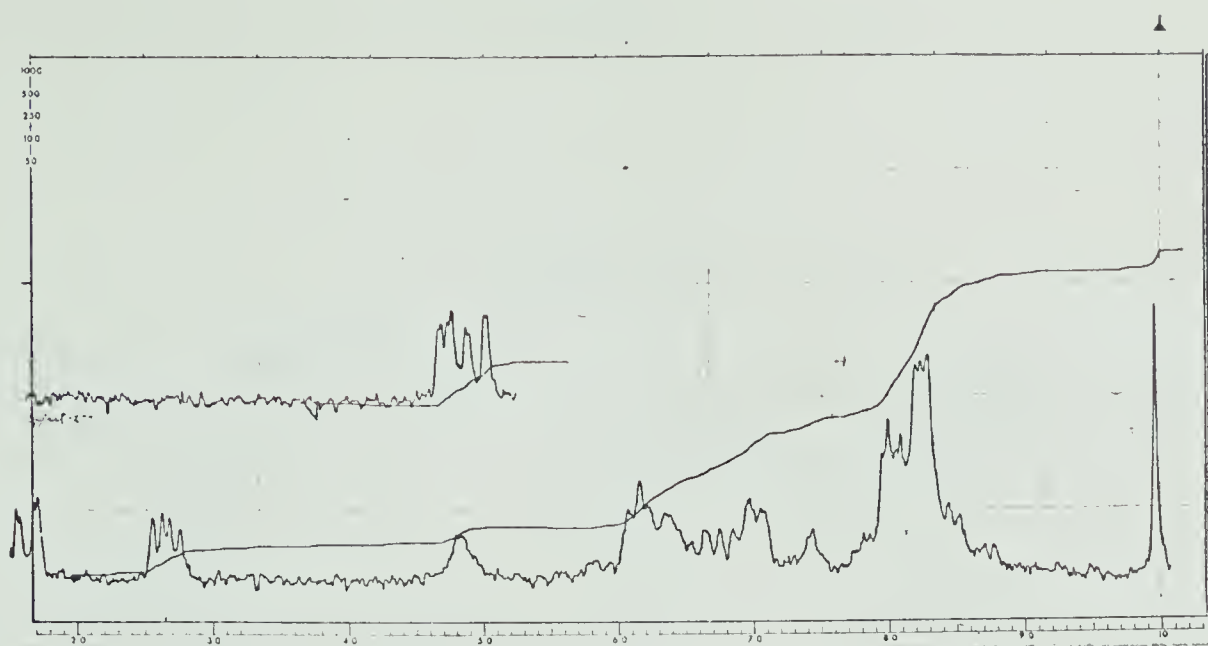


Fig. 9 The Hydroxy Imine 101

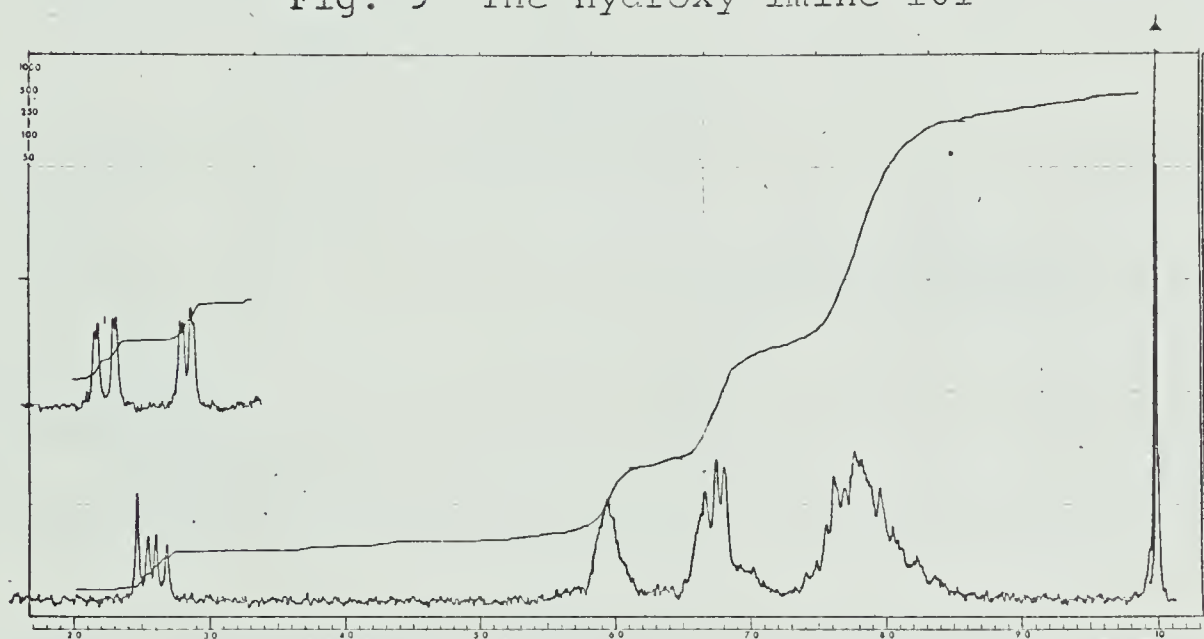


Fig. 10 The Imine 98

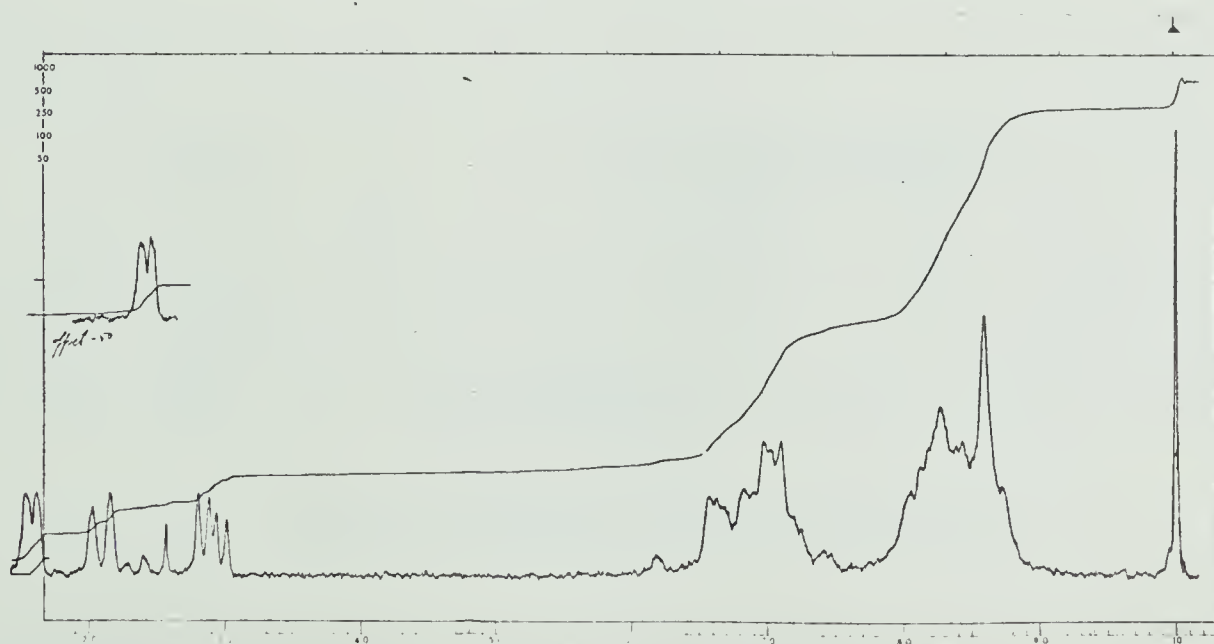


Fig. 11 The Amine 118





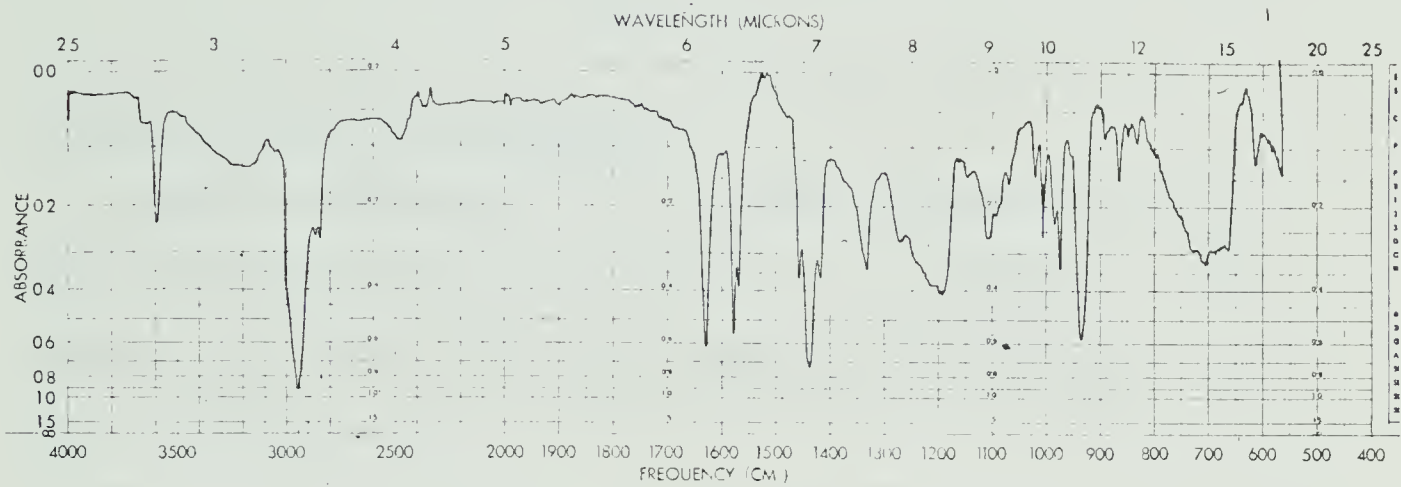


Fig. 12 The Hydroxy Imine 101

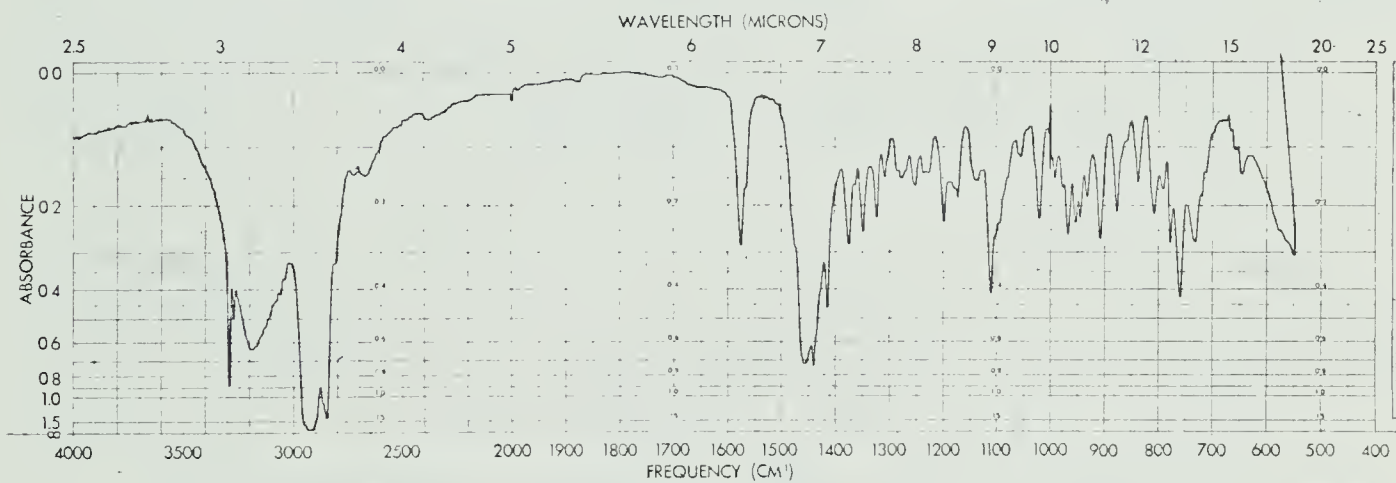


Fig. 13. The Hydroxy Amine 107 or 108 (main isomer)

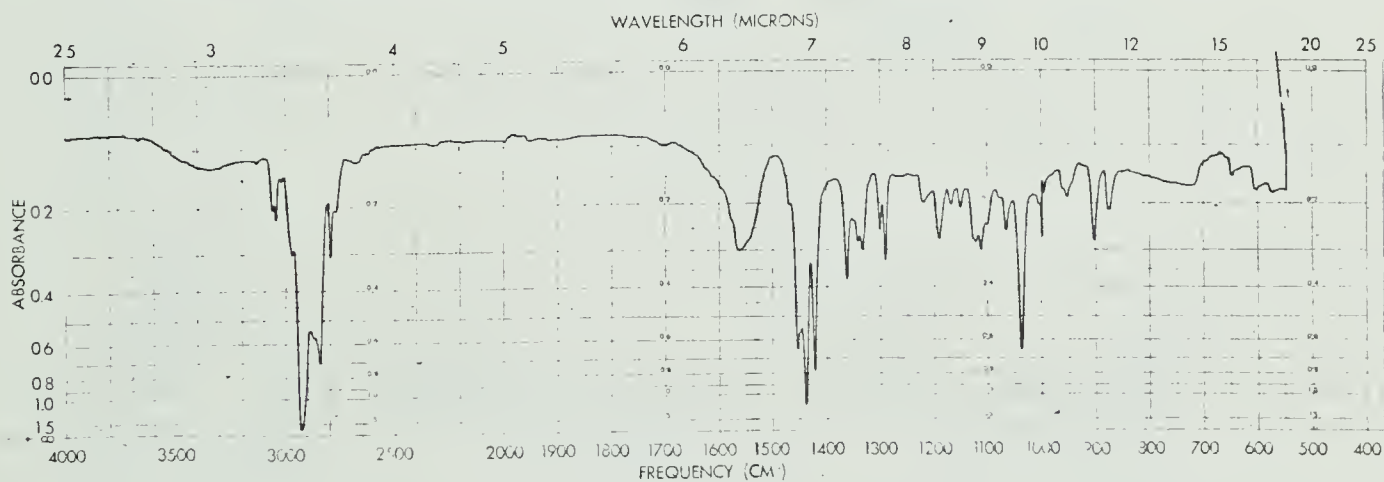


Fig. 14 The N-Methylamine 119

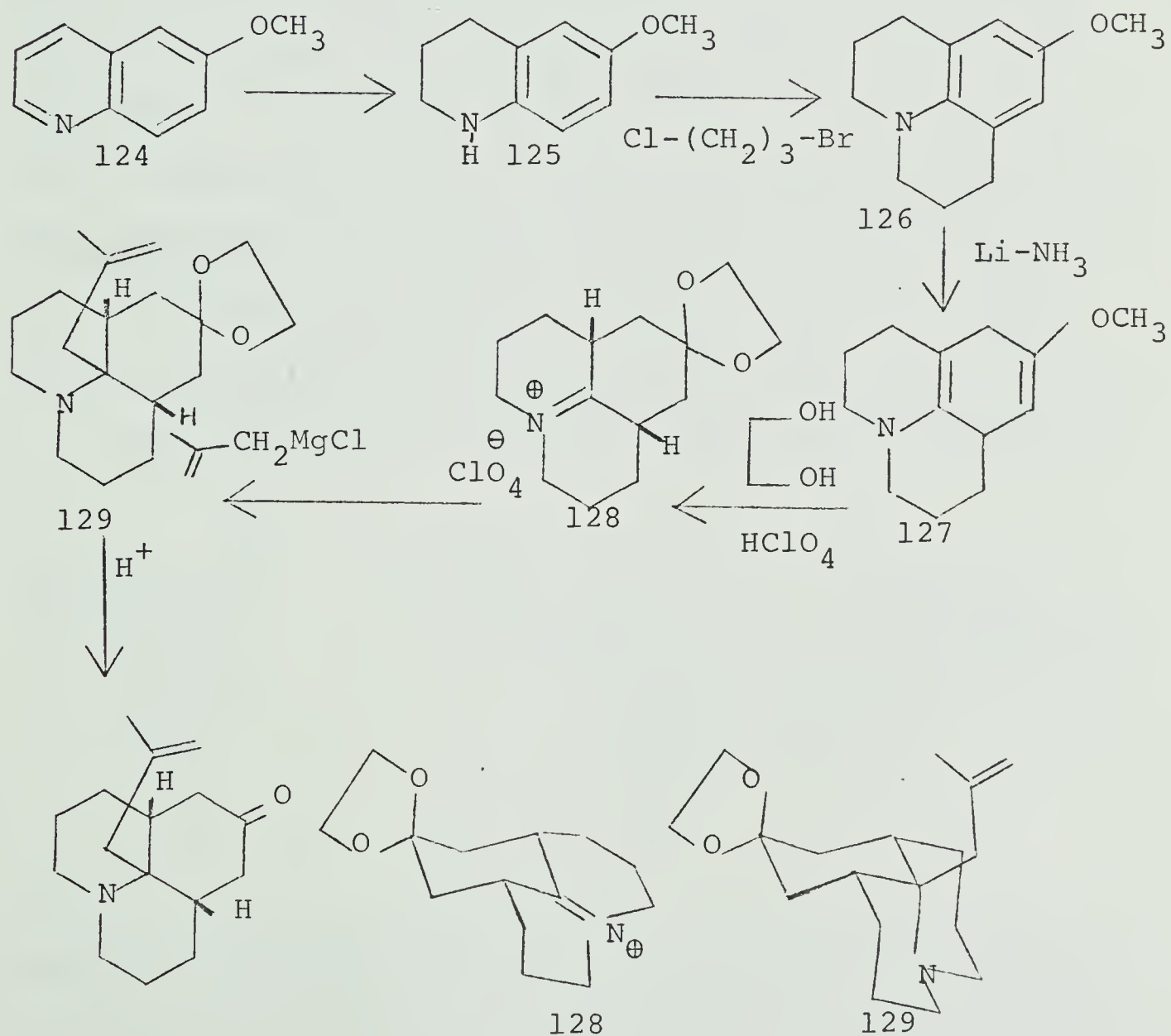


# Discussion and Results

## Part 3

### The Synthesis of Lycopodine.

Earlier research <sup>39,62</sup> in these laboratories had been carried out on the synthesis of lycopodine. The portions of this work to be used in the synthesis are shown in scheme 10.

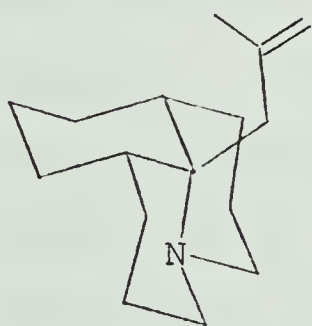


Scheme 10.

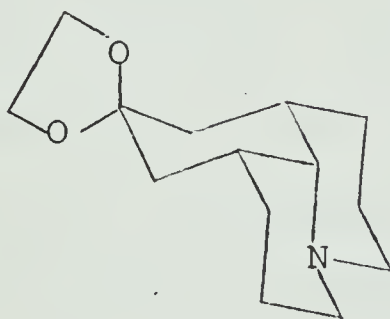


The starting point for this synthesis was 6-methoxyquinoline (124) which was reduced with hydrogen in the presence of Adams' catalyst to thalline (125). In order to circumvent the use of the expensive platinum oxide as the hydrogenation catalyst, the use of 5% rhodium on alumina <sup>62</sup> was investigated but this catalyst was found to be less efficient. Thalline (125) was treated with 1-bromo-3-chloropropane to give 9-methoxyjulolidine (126). An improved method for this step was developed. 9-Methoxyjulolidine (126) <sup>39</sup> was converted to the immonium salt 128. Treatment of the immonium salt 128 with methallylmagnesium chloride in tetrahydrofuran gave a mixture of products. Careful separation using column chromatography on alumina gave four pure components.

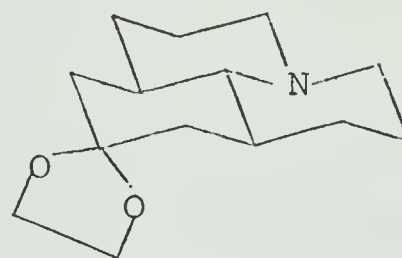
The least polar component isolated was compound 130



130



131



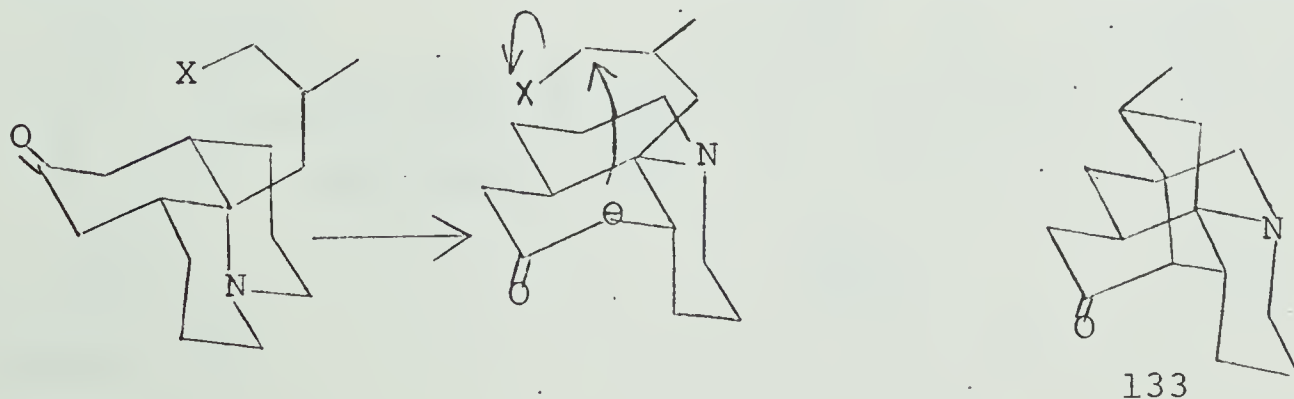
132

which was shown by infrared, nmr, and mass spectrum to be identical with authentic material <sup>62</sup>. The next component eluted was the major one, and proved to be the methallyl



ketal 129. Two more polar (i.e. lower  $R_F$ ) components were isolated in minor quantities. These had identical mass spectra and showed Bohlmann bands in their infrared spectra. The nmr spectra indicated that no methallyl group was present, only the ketal methylenes showing low field absorption. The less polar compound was identical to an authentic sample of 131 prepared by catalytic reduction<sup>39</sup> of the immonium salt 128. The more polar compound is therefore assigned the structure 132 as it is the only other hexahydrojulolidine which has two trans diaxial hydrogens  $\alpha$  to the nitrogen, and can thus show Bohlmann bands in the infrared.

The methallyl ketal 129 was shown<sup>39,67</sup> to possess the cis-cis structure shown. The presence of strong Bohlmann bands in the 2700-2800  $\text{cm}^{-1}$  region of the infrared indicates either a cis-cis or a trans-trans stereochemistry at the ring junctions. The fact that it reacts very sluggishly with methyl iodide ruled out the trans-trans system. This was the expected product on theoretical grounds since it results from addition of the Grignard



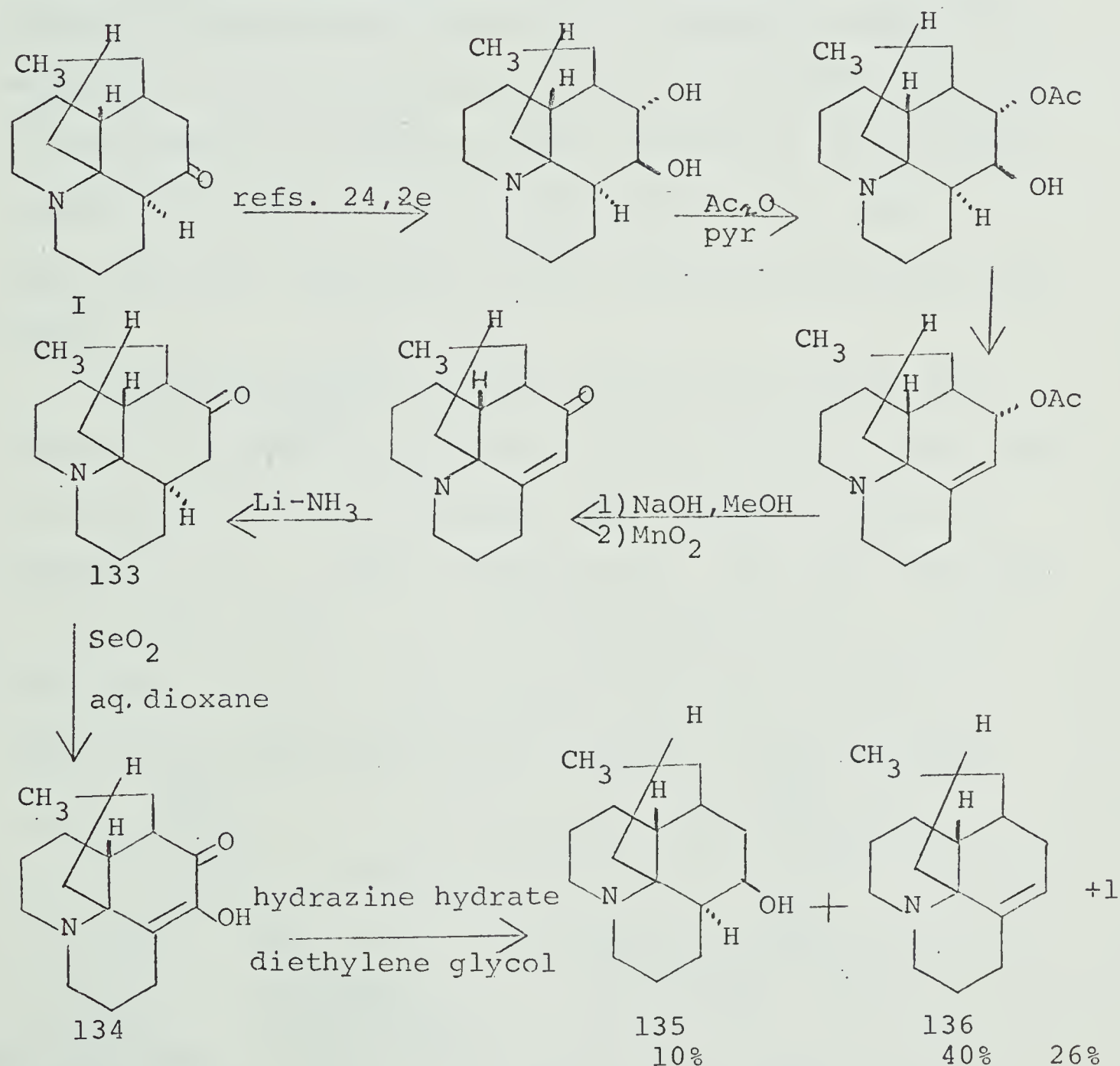
Scheme 11.





reagent to the less hindered side of the salt 128.

The general route for the synthesis as planned is shown in scheme 11. This involves first introduction of a suitable functional group in the side chain and then conversion of the cis-cis hexahydrojulolidine skeleton into a cis-trans hexahydrojulolidine skeleton.

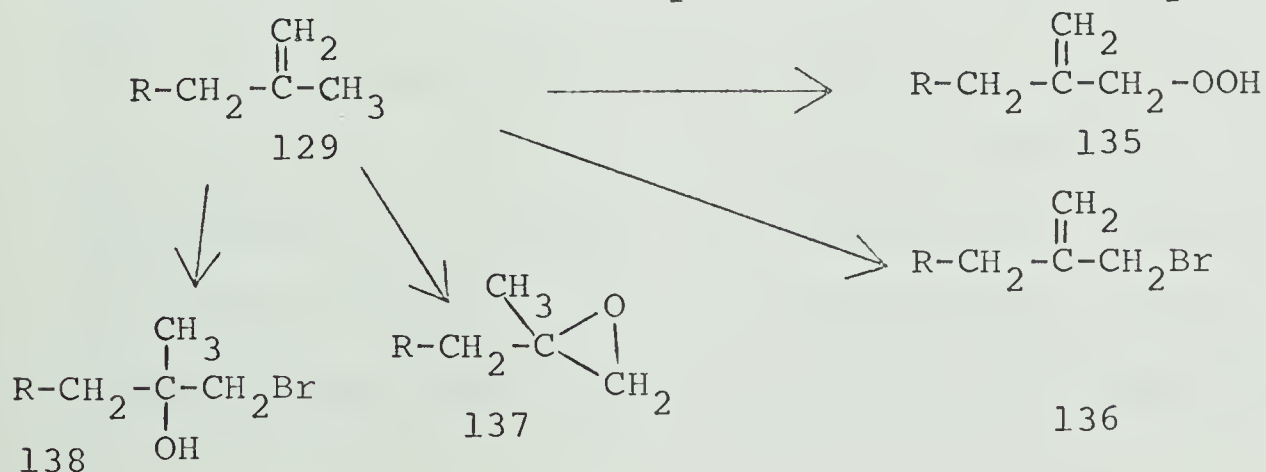


Scheme 12.



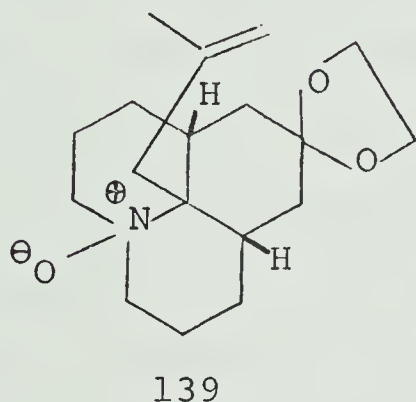
Base catalysed ring closure would then lead to the ketone 133. Ketone 133 has the carbonyl function at C<sub>6</sub> whereas in lycopodine it is at C<sub>5</sub>. Therefore, concurrent with this research the ketone 133 was prepared from lycopodine and then converted back to lycopodine by Dr. T. C. Joseph. The ketone 133 thus acts as a natural relay. The inter-conversion carried out by Dr. T. C. Joseph is outlined in scheme 12. The diosphenol 134 on Wolff-Kishner reduction in the absence of added base gave lycopodine (1), dihydrolycopodine (135), and anhydrodihydrolycopodine (136). The latter two compounds are also naturally occurring alkaloids.

The first problem in the synthesis was the introduction of a functional group on the side chain which could be suitable for base catalysed ring closure as shown in scheme 11, i.e., a good leaving group. The first idea was to leave the olefin, or a functional group at C<sub>15</sub> in the side chain to allow conversion of the methyl group to the correct stereochemistry at the end of the synthesis.





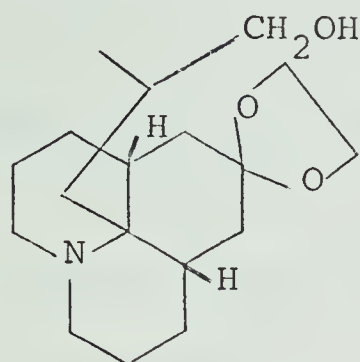
Photolysis <sup>64</sup> of the methallyl ketal 129 in the presence of oxygen using hematoporphyrin as initiator in the hope of obtaining 135, gave only starting material. Bromination <sup>65</sup> of 129 with N-bromosuccinimide in the hope of obtaining 136 gave similar results. Attempted addition of hypobromous acid <sup>66</sup> to the olefin 129 in the hope of obtaining 138 gave intractable material. In the hope of obtaining the epoxide, the use of m-chloroperbenzoic acid was attempted but the N-oxide 139 was obtained. An attempt to oxidise the N-oxide 139 to obtain the epoxide ended in failure.



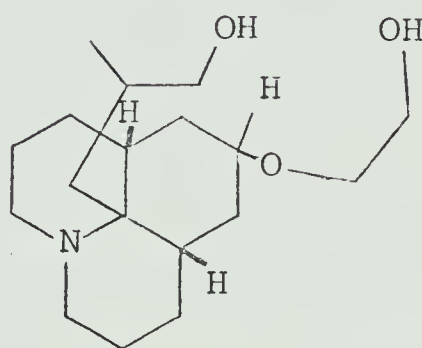
Since these methods designed to retain control of the stereochemistry at C<sub>15</sub> had failed, the more obvious diborane hydroxylation <sup>68</sup> was attempted. The diborane was generated from sodium borohydride and boron trifluoride-etherate in "diglyme" and bubbled into a solution of the methallyl ketal 129 in tetrahydrofuran. A 90% yield of the hydroxy ketal 140 was obtained after peroxide



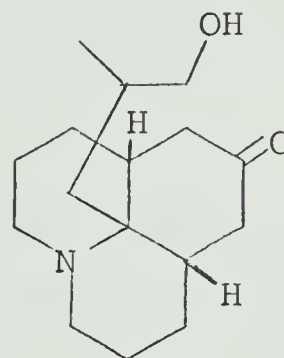
oxidation. Shorter reaction time yielded starting material while longer reaction times gave a new product which was shown to be 141.



140



141



142

141 showed hydroxyl absorption in the infrared. As confirmation of the structure of 141, it was acetylated to give the diacetate. The two acetyl methyls were clearly observed in the nmr spectrum, and the mass spectrum showed that the ethylene ketal had been cleaved. The by-product is presumed to arise by reductive cleavage with diborane.

Hydrolysis of the hydroxy ketal 140 gave the hydroxy ketone 142 which clearly showed Bohlmann bands at 2700-2800  $\text{cm}^{-1}$  in the infrared, indicating that it still possessed the cis-cis-hexahydrojulolidine skeleton.

It can be seen from the conformational drawing 144 that ring closure to the bicyclo [3.3.1] nonane system of lycopodine is impossible from this conformation. The possibility that 144 exists in the highly strained conformationally inverted form is rendered highly unlikely by





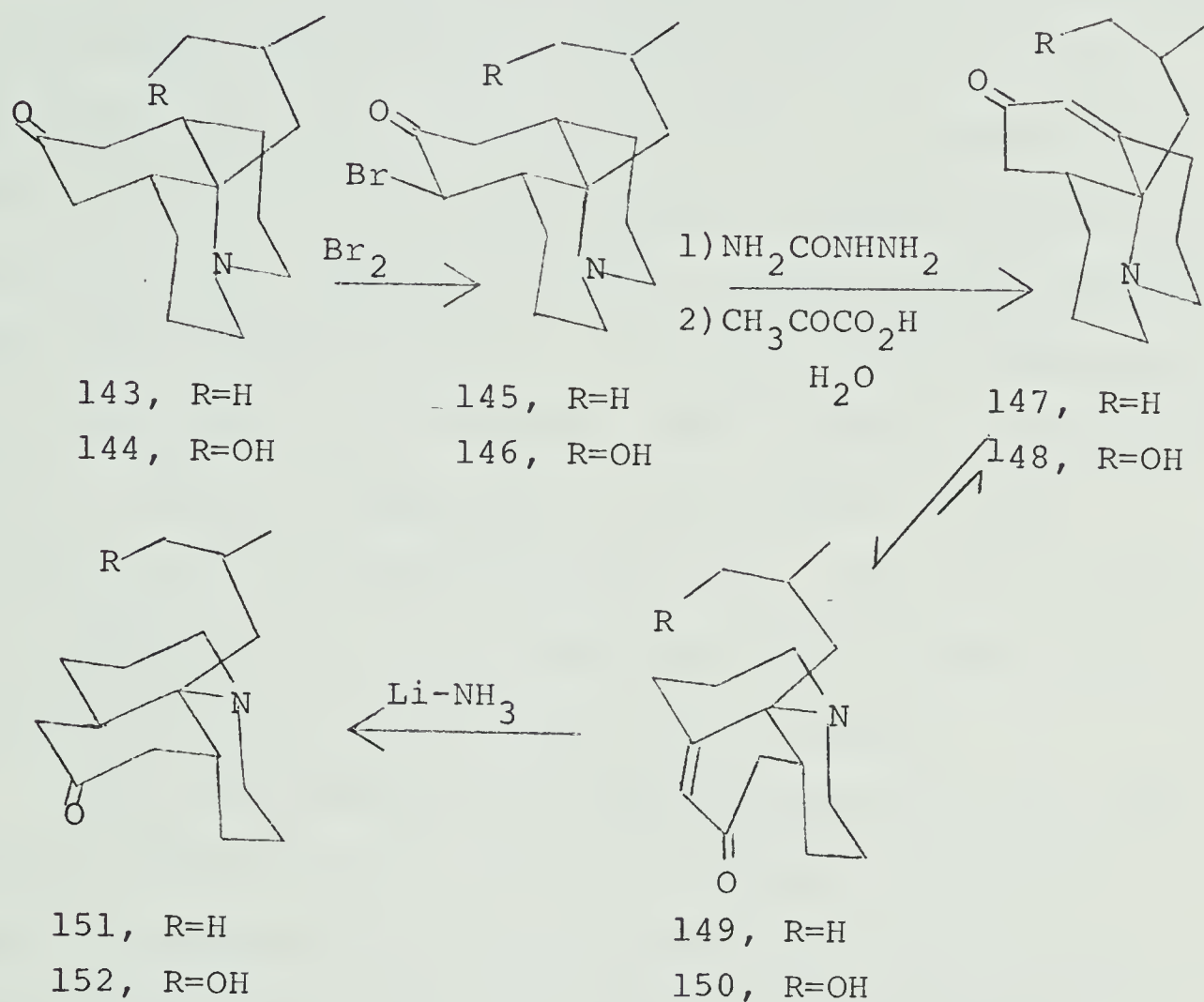
the presence of Bohlmann bands in the infrared spectrum. In order to make this synthetic route a feasible path to lycopodine it was necessary to develop a method for transforming cis-cis-hexahydrojulolidines of type 144 into cis-trans compounds such as 152.

Concurrent with the studies on the hydroxyl compound a simpler substrate 143, prepared by catalytic hydrogenation of the methallyl ketal 129, was studied by A. C. Soper<sup>62</sup>. It was felt that the isomerisation might be accomplished via an  $\alpha,\beta$ -unsaturated ketone. Because of the conformational mobility at the nitrogen it should be possible for the ketone 147 to assume the other conformation 149 (similarly 148 $\rightarrow$ 150). This change involves inversion of ring A at the nitrogen and transformation of the resultant boat into a new chair with simultaneous transformation of the unsaturated ring from one half-chair to the other half-chair. An examination of models indicated that 149 and 150 might in fact be the favoured conformation for the unsaturated ketone.

The plan for the isomerisation of ketone 143 and 144 to 151 and 152 is outlined in scheme 13. While the hydroxyl series ran into some problems, the ketone 143 was converted<sup>62</sup> to 151. Both 143 and 151 had identical mass spectra, but the infrared spectra differed in that 143 had Bohlmann bands at 2700-2800  $\text{cm}^{-1}$  as mentioned, and 151



showed no Bohlmann bands at all. The two ketones also showed different chromatographic behavior. The  $\alpha,\beta$ -unsat-



Scheme 13

urated ketone isolated did not show Bohlmann bands indicating that 149 is the preferred conformation over 147. After these experiments it was clear that this method could be used successfully to isomerise cis-cis-hexahydrojulolidines to cis-trans-hexahydrojulolidines.

The hydroxy ketone 144 was smoothly brominated <sup>2e</sup> to the bromoketone 146. As the bromoketone was not stable

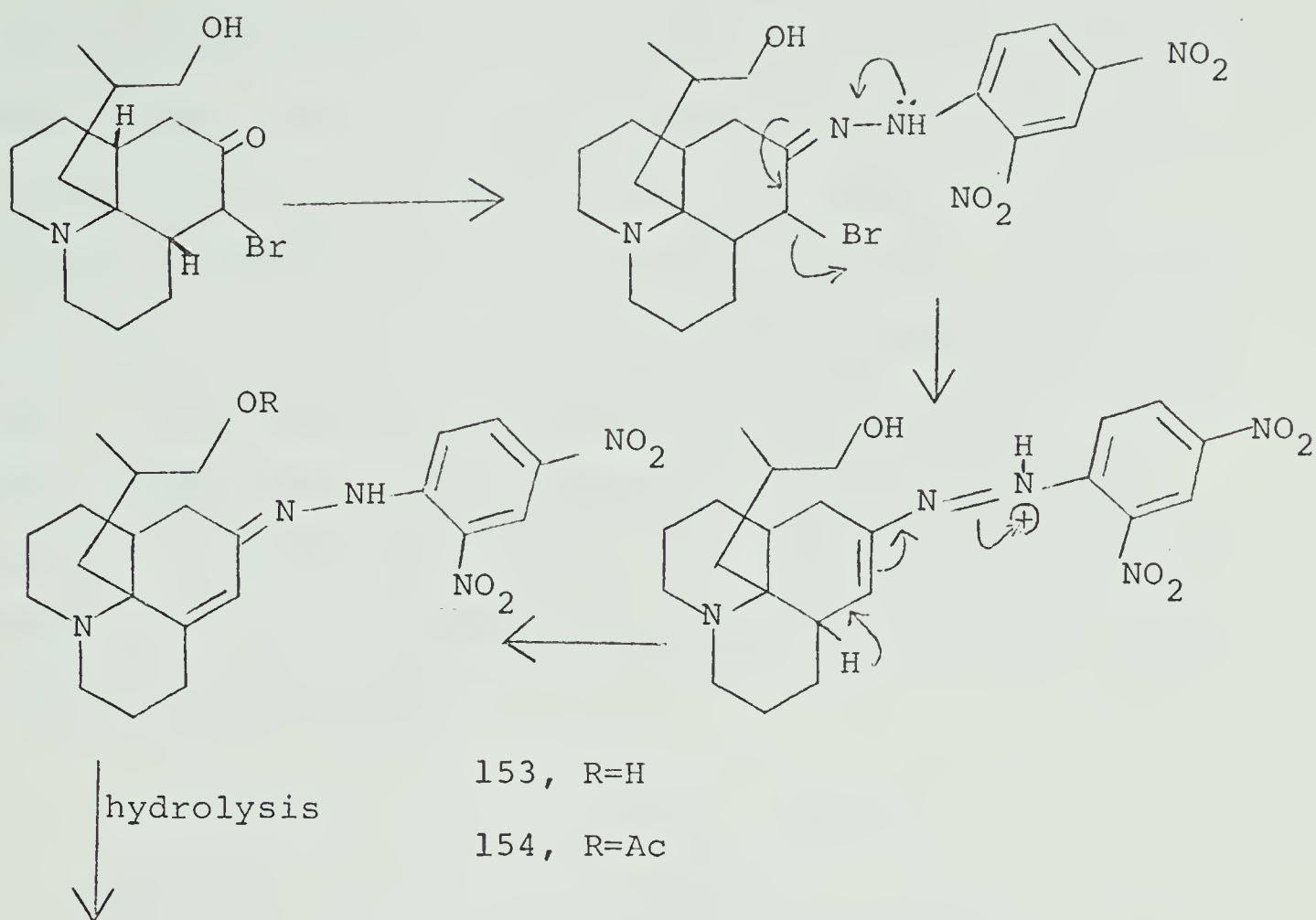


as the free base, the hydrobromide salt resulting from the reaction was used in further reactions. The hydrobromide was not crystalline but its identity was confirmed by infrared, which showed a shift in the carbonyl absorption from  $1712\text{ cm}^{-1}$  to  $1736\text{ cm}^{-1}$ , and absorption in the nmr at  $\tau$  3.75 for the hydrogen  $\alpha$  to the carbonyl and bromine. The coupling constant (J) was 13 cps, indicating that the hydrogen at  $C_7$  was trans to the hydrogen at  $C_{12}$  (or  $C_5$  and  $C_4$ ) i.e.  $180^\circ$ . This reaction introduces a second element of asymmetry in the molecule as the bromine can be introduced at  $C_7$  or  $C_5$ . The other centre of asymmetry is at  $C_{15}$ . From this step on there are two diastereoisomers each having d and l isomers.

The normal methods for dehydrobromination (i.e. the use of tertiary bases such as collidine) could not be applied successfully because trans diaxial elimination is required and the bromo ketone 146 has the bromine cis and equatorial to the hydrogen. Dehydrobromination with lithium bromide <sup>69</sup> and lithium carbonate in dimethylformamide gave intractable material.

A dehydrobromination reaction where the steric arrangement is unimportant in the formation of the  $\alpha,\beta$ -unsaturated-2,4-dinitrophenylhydrazone <sup>70</sup> and subsequent hydrolysis of the hydrazone as shown in scheme 14.





Scheme 14.

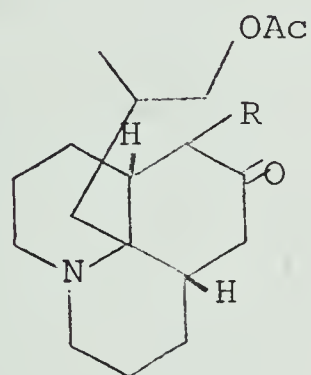
Treatment of the hydroxybromoketone 146 with 2,4-dinitrophenylhydrazine gave red crystals of the free base 154 instead of 153 as expected. As the reaction is carried out in boiling glacial acetic acid, the hydroxyl group is acetylated as shown by absorption at  $1720\text{ cm}^{-1}$  in the infrared spectrum and by a three proton singlet at  $\tau\ 7.90$  in the nmr spectrum. The newly introduced olefin showed absorption at  $1610\text{ cm}^{-1}$  in the infrared, and  $\tau\ 3.8$  in the nmr spectrum.

The hydroxy ketone 142 was acetylated to give the



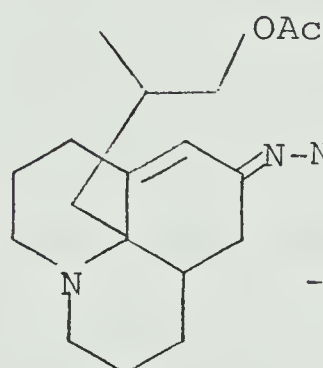


acetoxy ketone 155 before the above reaction was repeated. The acetoxy ketone 155 was brominated as before to give an acetoxy bromoketone hydrobromide 156. Treatment with 2,4-dinitrophenylhydrazine again yielded 154. Hydrolysis of 154 was attempted first with acetone and hydrochloric acid <sup>71</sup> and then with pyruvic acid and hydrobromic acid <sup>70</sup>. Both methods gave a poor yield of an uncharacterisable product which was certainly not the desired  $\alpha,\beta$ -unsaturated ketone 159. This approach was abandoned in favour of the semicarbazide method.

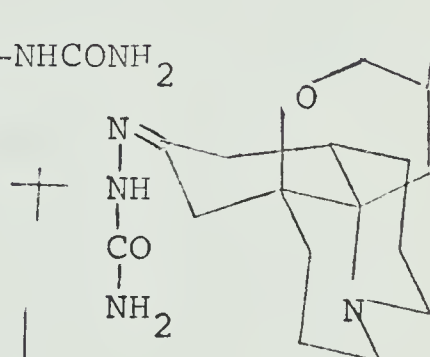


155, R=H

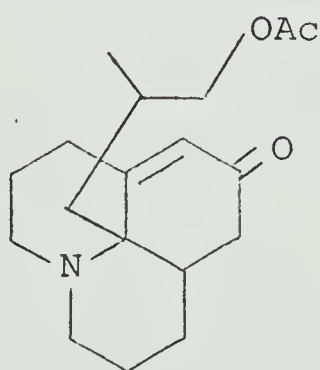
156, R=Br



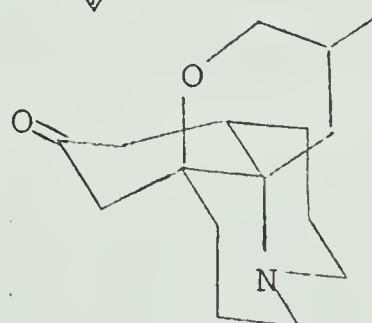
157



158



159



160



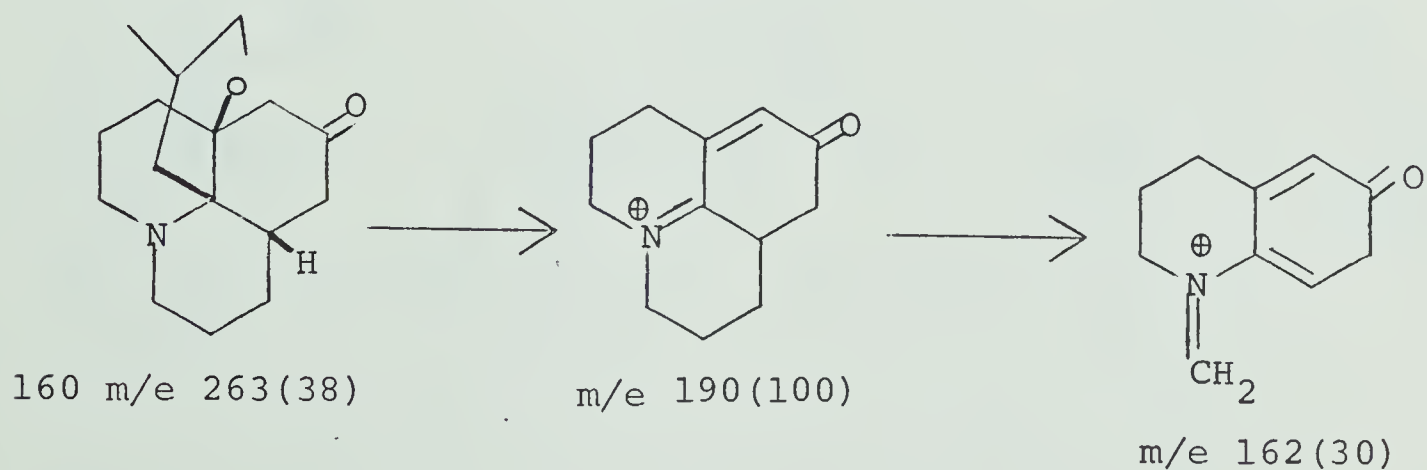
Treatment of the acetyl bromoketone hydrobromide 156 with semicarbazide <sup>72</sup> in chloroform and tertiary butyl alcohol gave a mixture of two non crystalline products (by tlc). A small quantity of each material was separated by column chromatography. One product was the expected acetyl  $\alpha,\beta$ -unsaturated semicarbazone 157 with absorption at 275 m $\mu$  in the ultraviolet spectrum and a one proton absorption at  $\tau$  4.18 for the olefinic proton in the nmr spectrum. Spectral data for this type of compound are somewhat lacking in the literature so a model compound was prepared from methyl vinyl ketone. The ultraviolet, infrared, and nmr spectra of the  $\alpha,\beta$ -unsaturated semicarbazone part of the molecule were almost identical to that found in 157. The second product showed absorption at 230 m $\mu$  in the ultraviolet spectrum, characteristic of a semicarbazone. The imine absorption in the infrared was shifted from 1555 cm<sup>-1</sup> to 1550 cm<sup>-1</sup>. The infrared spectrum showed absorption at 1075 cm<sup>-1</sup> for an ether but lacked the acetyl absorption at 1730 cm<sup>-1</sup>. The product was assumed to be 158 after its hydrolysis product had been identified.

Treatment of the acetyl bromoketone hydrobromide 156 with semicarbazone in boiling acetic acid <sup>73</sup> gave the same mixture as before. This time instead of isolating the products, pyruvic acid and water were added to the



refluxing solution and the hydrolysis products isolated. The product was a mixture of two compounds with almost identical  $R_F$  values on tlc which could not be separated by column chromatography. One compound was obviously the  $\alpha,\beta$ -unsaturated ketone 159 because the ultraviolet spectrum of the mixture showed absorption at 244 m $\mu$ , the infrared spectrum showed absorption at 1615 and 1665  $\text{cm}^{-1}$  for an  $\alpha,\beta$ -unsaturated ketone, and the nmr showed a one proton absorption at  $\tau$  4.09. The other product was later shown to be 160. The mass spectrum of the mixture showed peaks for both compounds.

It was thought that hydrolysis of the acetate would allow separation of the  $\alpha,\beta$ -unsaturated ketone from the other component by virtue of its increased polarity with a hydroxyl function in place of the acetate. However, after hydrolysis the other component was the sole product. Base treatment had therefore converted the acetyl  $\alpha,\beta$ -unsaturated ketone 159 to the ether 160. This now allowed

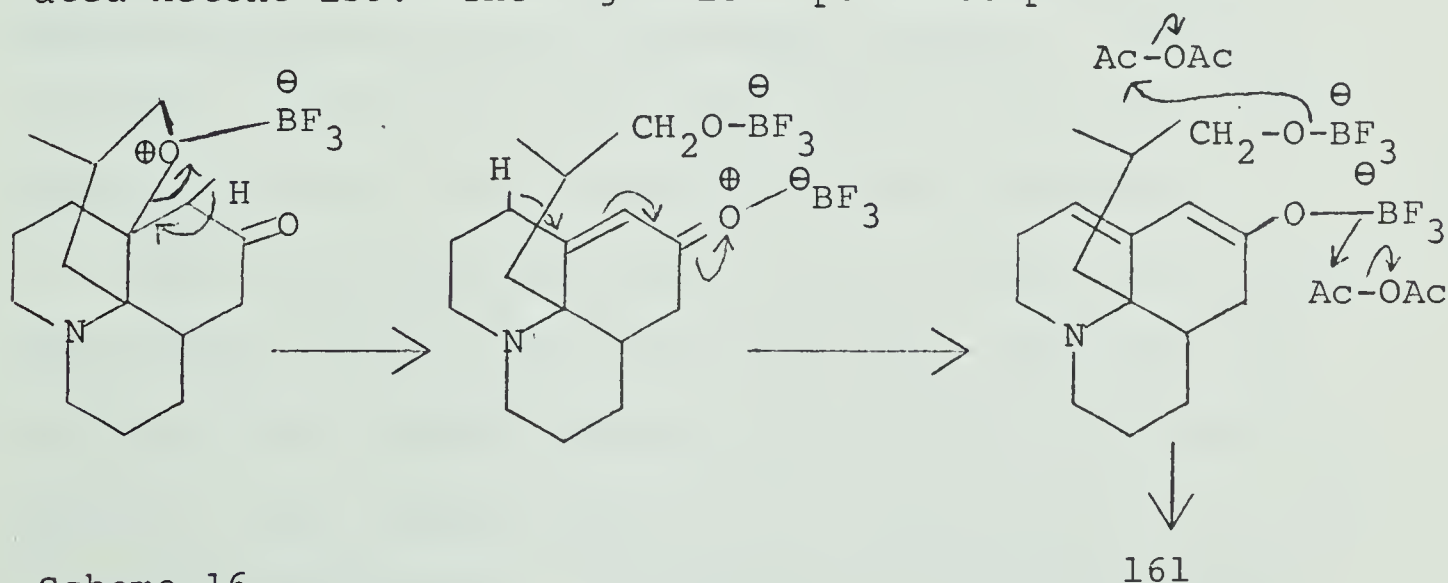


Scheme 15



characterisation of the ether 160. The infrared spectrum showed normal ketone absorption at  $1715\text{ cm}^{-1}$ , very strong Bohlmann bands and an ether absorption at  $1075\text{ cm}^{-1}$ . The mass spectrum shown in scheme 15 is reminiscent of the lycopodine type fragmentation because the side chain is joined to the ring skeleton in two places. It therefore fragments to give a base peak at  $m/e$  190 whereas all the other compounds give  $m/e$  192 (except where there is an  $\alpha,\beta$ -unsaturated ketone).

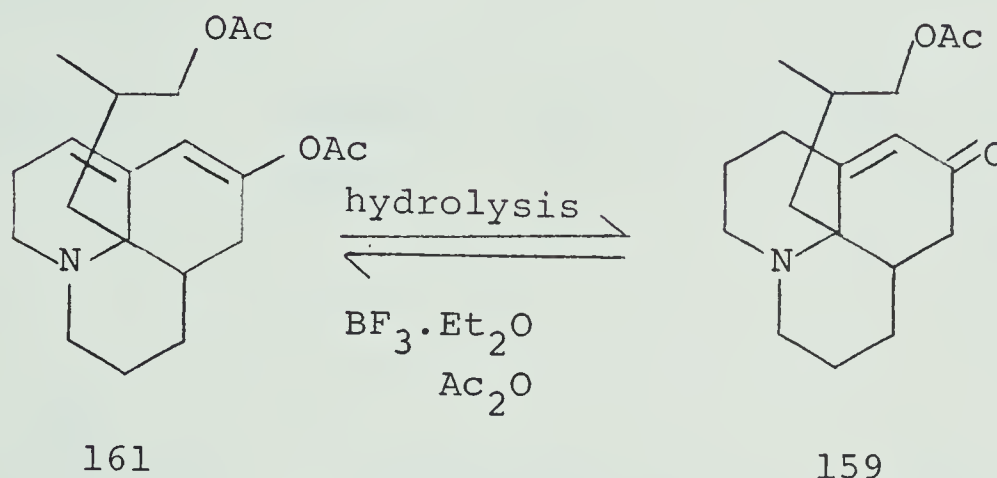
As a final proof of the structure, the ether 160 was treated with acid. It was thought that acid would reverse the basic ring closure. Hydrochloric acid had no effect but boron trifluoride-etherate in acetic anhydride <sup>67,74</sup> converted the ether 160 to a mixture of two components. They were separated by column chromatography. The more polar compound proved to be the desired acetyl  $\alpha,\beta$ -unsaturated ketone 159. The major less polar component was the







enol acetate 161 of 159. The reaction is thought to take place as shown in scheme 16. 159 could arise either from hydrolysis of the enol acetate 161 during the work up or from the reaction itself if the  $\alpha,\beta$ -unsaturated ketone does not react further with the boron trifluoride.

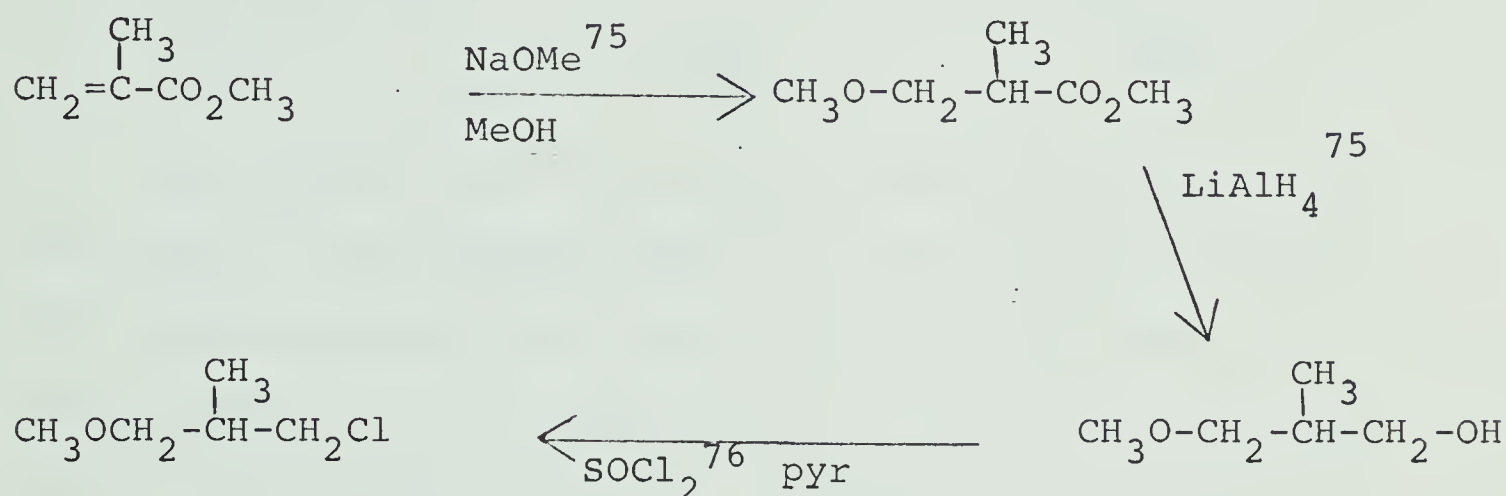


The conversion to the  $\alpha,\beta$ -unsaturated ketone 159 did not proceed in high yield so it was decided to reduce the dehydrobromination mixture directly and then to separate the various components. Lithium-ammonia reduction however gave an intractable product. Various reaction conditions were investigated without any great success so this route to lycopodine was abandoned.

The  $\alpha,\beta$ -unsaturated ketone 149 is reduced by lithium and ammonia without difficulty so there appeared to be no reason why another stable group should not be satisfactory. The acetyl group is not satisfactory, since it undergoes ammonolysis. The group used must be readily



converted to a suitable leaving group. A methyl ether seemed to suit the purpose. To circumvent the difficulty of forming a methyl ether from the hydroxyl compound a new Grignard reagent incorporating the methyl ether was used. 1-Chloro-2-methyl-3-methoxypropane was prepared as shown in scheme 17.

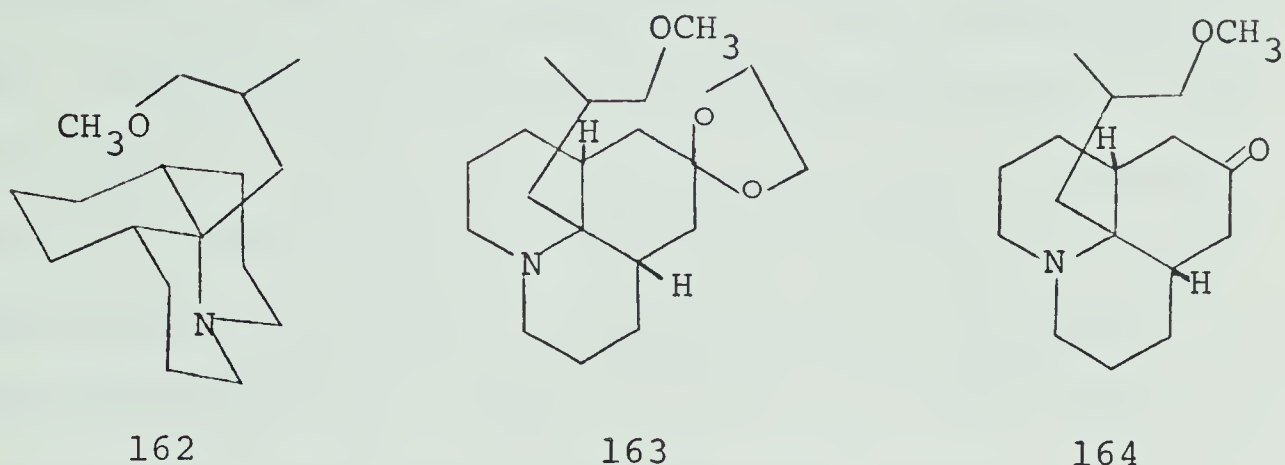


Scheme 17.

The Grignard reagent from 1-chloro-2-methyl-3-methoxypropane could not be prepared in tetrahydrofuran but was readily prepared in diethyl ether. Before addition of the immonium perchlorate 128 the ether was replaced with tetrahydrofuran. A mixture of products was obtained as before. The mixture was separated into three components by column chromatography. The less polar component was shown to be 162, corresponding to 130. It showed Bohlmann bands in the infrared spectrum but no ethylene ketal was



observed in the infrared or nmr spectra.



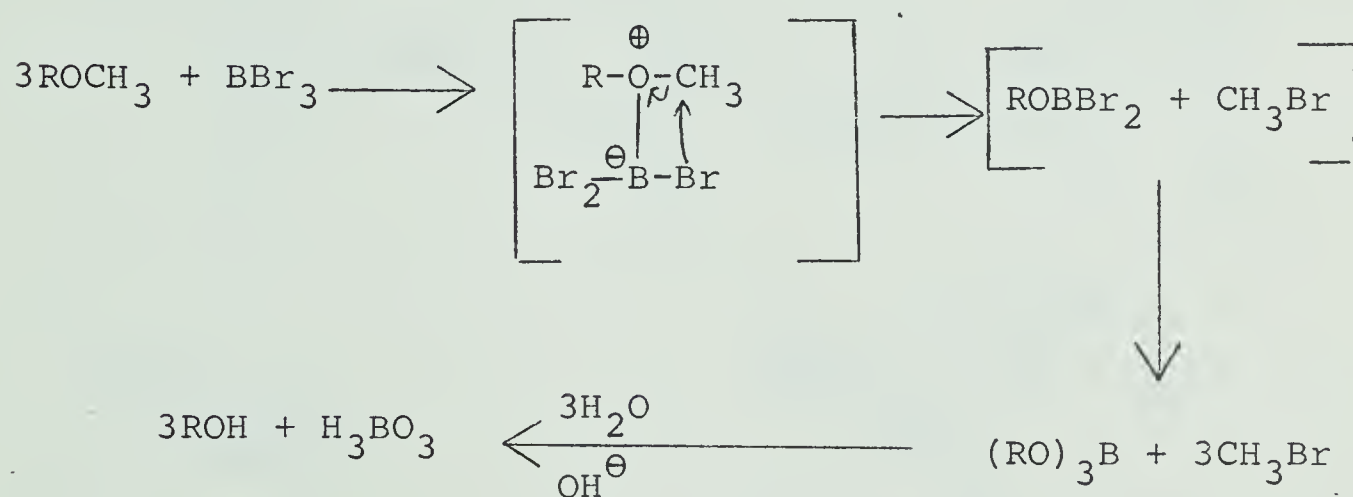
The compound 131 was also isolated and proved to be the same as the compound from the first Grignard reaction. The required product 163 was isolated in 70% yield. At this stage it was discovered that repeated recrystallisation of the immonium salt 128 eliminated the formation of the two side-products. The salt was recrystallised from methanol until the filtrate was colourless (approx. five times). When this purified immonium salt was used an almost quantitative yield of the methoxy ketal 163 was obtained. The side-products therefore seem to arise out of impurities in the immonium salt 128 rather than through side reactions during the Grignard reaction.

The methoxy ketal 163 was smoothly hydrolysed to the methoxy ketone 164. Both methoxy compounds showed Bohlmann bands in the infrared spectrum indicating the cis-cis-hexahydrojulolidine structure. Before attempting to invert the stereochemistry a method for cleaving the



methyl ether was sought. Cleavage of the methyl ether would also confirm the structure of the methoxy ketone 163. Treatment with boron trifluoride etherate <sup>77</sup> did not result in ether cleavage but gave the enol acetate of 163 instead. Both enol acetate (1600 and 1760  $\text{cm}^{-1}$ ) and methoxyl (1110  $\text{cm}^{-1}$ ) absorptions were observed in the infrared spectrum. The nmr spectrum indicated that both methoxy and enol acetate groups were present. Basic hydrolysis gave back the starting material.

Boron tribromide has been reported <sup>78</sup> to cleave ethers to the corresponding alcohol and alkyl bromide. The reaction probably proceeds as shown in scheme 18.



Scheme 18

Boron triiodide <sup>79</sup> has been reported to act as shown in scheme 19. Treatment of the methoxy ketone 164 with boron tribromide in methylene chloride gave an almost quantitative yield of the hydroxy ketone 142 of known stereochemistry.



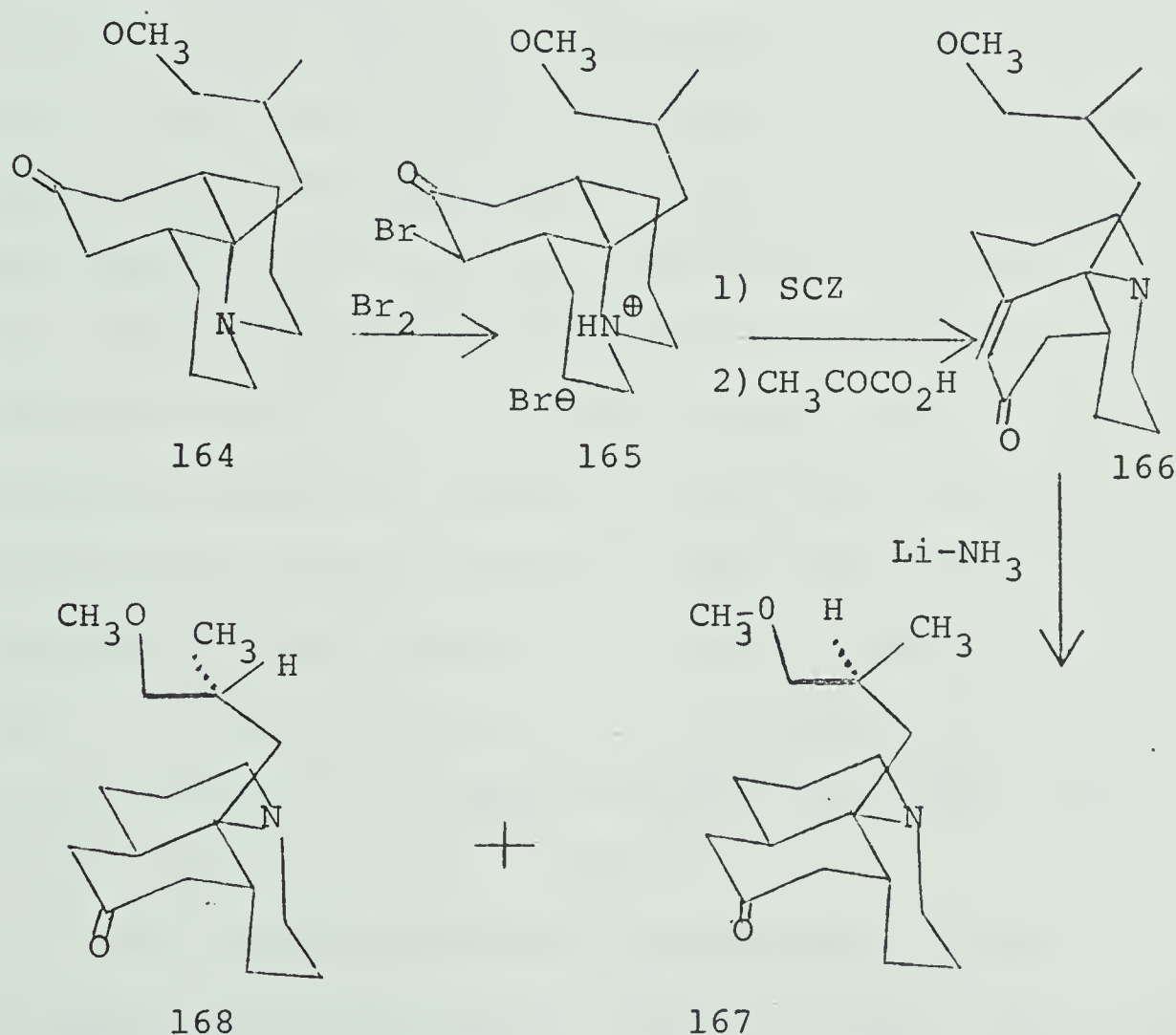




Scheme 19



The next step in the synthesis involved the isomerisation of the cis-cis-hexahydrojulolidine 164 to the cis-trans-hexahydrojulolidine structure. This was carried out by the previously elaborated methods and is outlined in scheme 20.



Scheme 20.



Some difficulty was encountered in the bromination <sup>2e</sup> of the methoxy ketone 164. The use of 1.3 equivalents of bromine gave optimum yields of the monobromo ketone. Less than this amount of bromine left unreacted starting material while a larger amount led to dibromination as shown by the absorption at  $1752\text{ cm}^{-1}$  in the infrared spectra.

The methoxy bromoketone hydrobromide 165 was treated with semicarbazide <sup>73</sup> (and pyruvic acid and water) in glacial acetic acid as in the acetoxy series. The product consisted of several components with very similar  $R_F$  values. These components could not be separated by any means. The two major components were assumed to be the methoxy  $\alpha,\beta$ -unsaturated ketone 166 and unreacted starting material 164. Absorption at  $1750\text{ cm}^{-1}$  in the infrared spectrum indicated that a minor component may be the enol acetate of 164 or 166. The ultraviolet spectrum showed absorption at  $244\text{ m}\mu$ , characteristic of the  $\alpha,\beta$ -unsaturated ketone. The infrared and nmr spectra also confirmed the presence of 166 as a major component ( $1625, 1680\text{ cm}^{-1}$  and  $\tau\ 4.30$ ).

The dehydrobromination mixture was reduced with lithium-ammonia to yield a mixture of two components in about equal proportions. They were separated by column chromatography. The less polar material was the mixture



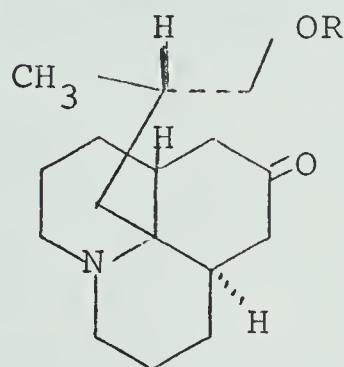
of methoxy ketones 167 and 168 ( $R_F$  values almost identical, only slightly separated on tlc). The more polar material was a mixture of the  $\alpha,\beta$ -unsaturated ketone 166 and the methoxy ketone 164. The latter was reduced again and chromatographed and the mixture thus obtained reduced and chromatographed again. The total methoxy ketones 167 and 168 were combined to give a yield of about 18% from the methoxy ketone 164 (with the cis-cis hexahydrojulolidine skeleton). The mass spectrum of the diastereoisomeric ketones 167 and 168 was almost identical to that of 164. The infrared spectrum did not show Bohlmann bands indicating they possess the cis-trans hexahydrojulolidine skeleton.

The ketones 167 and 168 are diastereoisomers, only one of which will lead to lycopodine, the other leading to  $C_{15}$ -epilycopodine. Due to the similarity in  $R_F$  values they could not be separated at this stage. The mixture was treated with boron tribromide as in the previous case.

A mixture of two compounds was obtained from the cleavage in about 60% yield. The yield is not as high as was obtained from the methoxy ketone 164. The lower yield may be caused by reaction of the now more exposed nitrogen with the boron tribromide or methyl bromide. It is also possible that cleavage gives some of the primary bromide

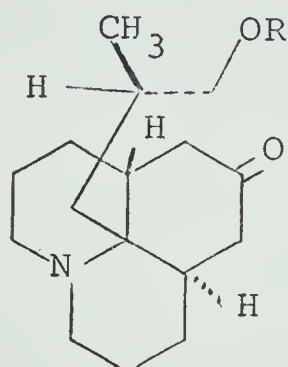


which ring closes on the nitrogen (as later shown with the tosylate) to form a quaternary salt which would remain in the aqueous layer in the work up. The mixture was separated by column chromatography to give between 5 and 20% of the less polar alcohol 169 and between 15 and 32% of the more polar alcohol 170. It was not possible to distinguish between 169 and 170 at this stage. The assignment of the structures follows from the transformation of 169 to a compound of established



169, R=H

171, R=Ac



170, R=H

172, R=Ac

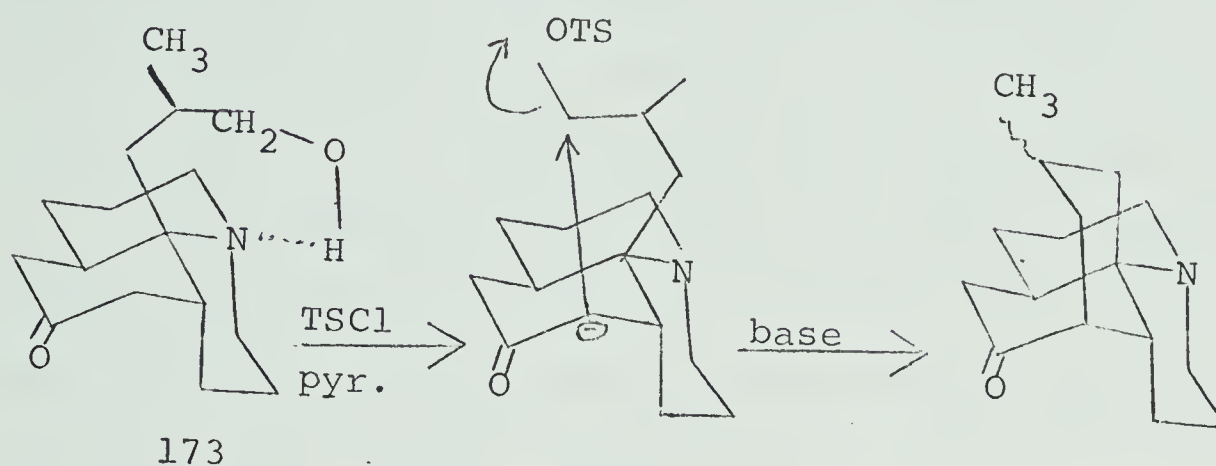
stereochemistry (i.e., one prepared from lycopodine). The mass spectra of 169 and 170 are very similar. The only major difference in the nmr spectra is the C<sub>16</sub> methyl absorption at  $\tau$  9.05 for 169 and at  $\tau$  8.96 for 170. The infrared spectra of both show the hydroxyl absorption as a poorly defined band centered at 3100 cm<sup>-1</sup>. This is probably due to extremely strong intramolecular hydrogen





bonding as shown in the configurational drawing 173.

The alcohols were acetylated to give 171 and 172, to confirm the presence of hydroxyl groups. The scheme for the rest of the synthesis as planned is outlined in scheme 21.



Scheme 21.

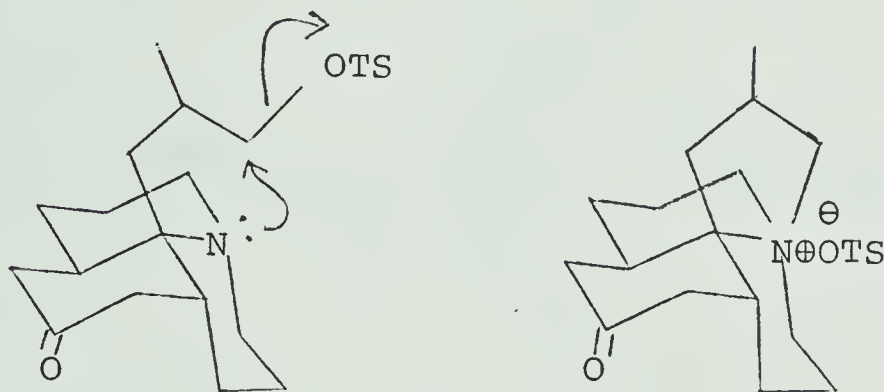
Alcohol 170 was treated with p-toluenesulphonyl chloride in pyridine. Work up in the usual manner provided no organic soluble material. The aqueous layer was therefore continuously extracted with methylene chloride. A nicely crystalline material was obtained and proved <sup>80</sup> to be 174. The nmr and infrared spectra <sup>80</sup> showed that a p-toluenesulphonyl anion was present. Alcohol 169 reacted in the same way as shown in scheme 22 to form a quaternary salt via internal ring closure on nitrogen.



It was obvious now that to prevent ring closure on nitrogen, the nitrogen had to be blocked.

The alcohol 144 was used as a model compound. It could not be induced to form a benzyl salt under even forcing conditions. The next method investigated is outlined in scheme 23. The alcohol 144 when treated with conc. hydrobromic acid gave the bromo hydrobromide 175.

It was hoped that when the salt 176 was treated with strong base that ring closure on carbon would occur more rapidly than ring closure on nitrogen. Treatment

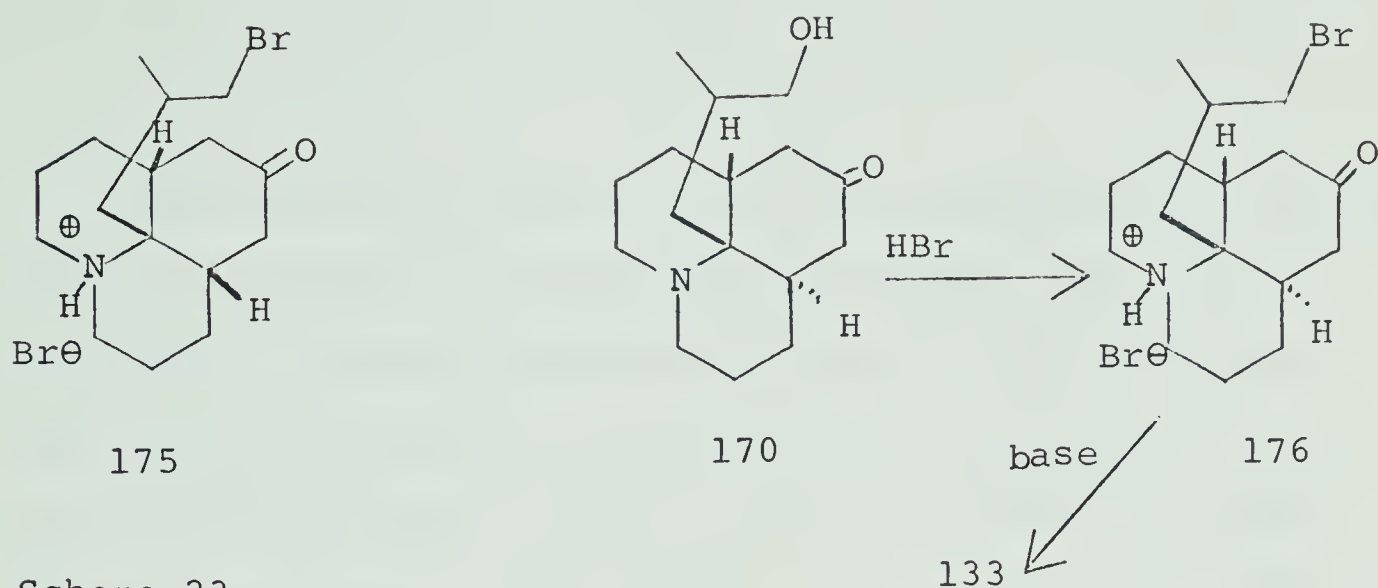


Scheme 22.

174

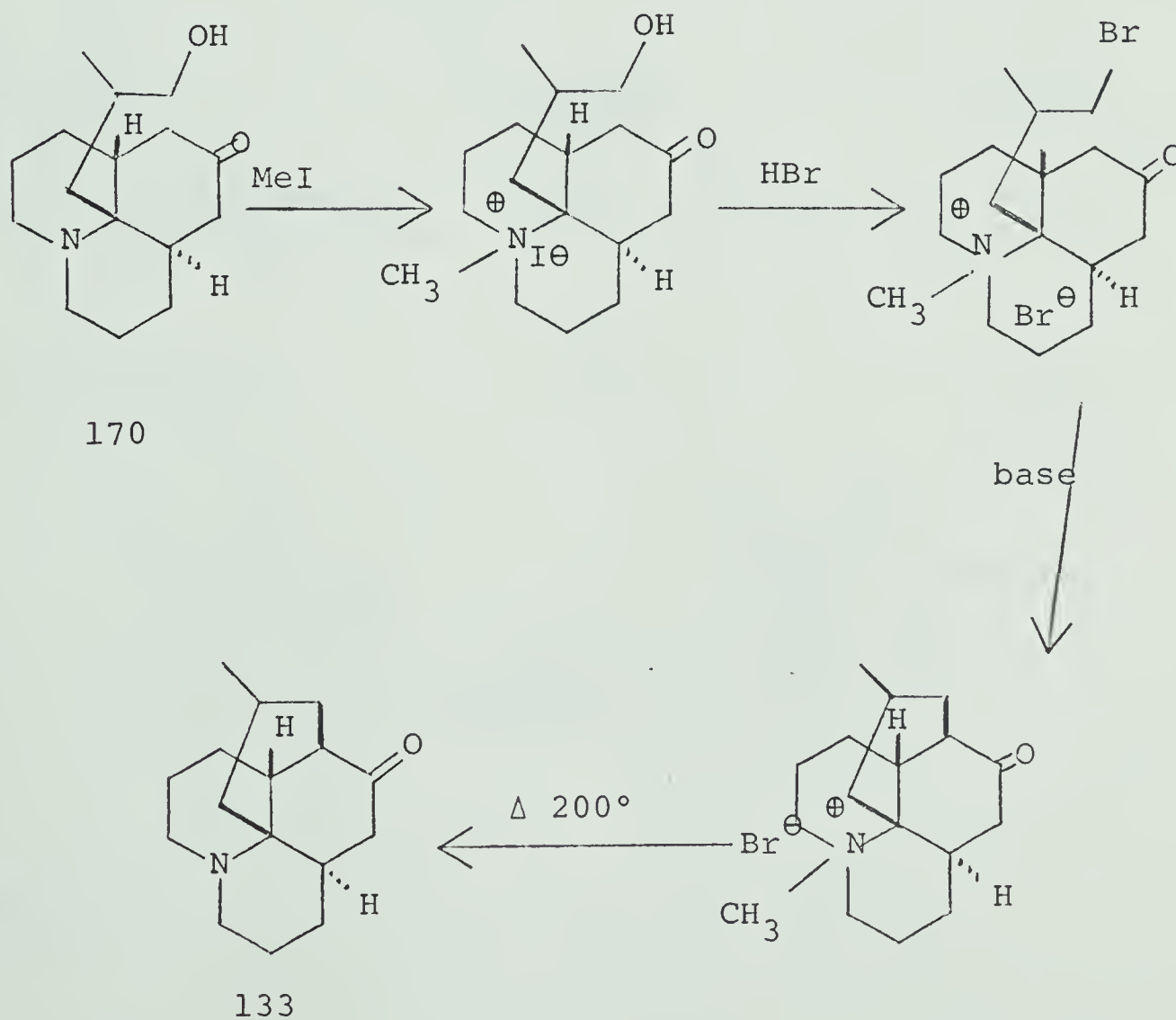
of 176 (represents both diastereoisomers) with potassium tertiary butoxide in tertiary butyl alcohol gave a 30% yield of basic material. The tlc of the product showed several components, one of which had an  $R_F$  value similar to that of the desired ring closed ketone 133. The mass spectrum also indicated the presence of ring closed material (peaks at  $m/e$  247 and  $m/3$  190). The yield of the





Scheme 23.

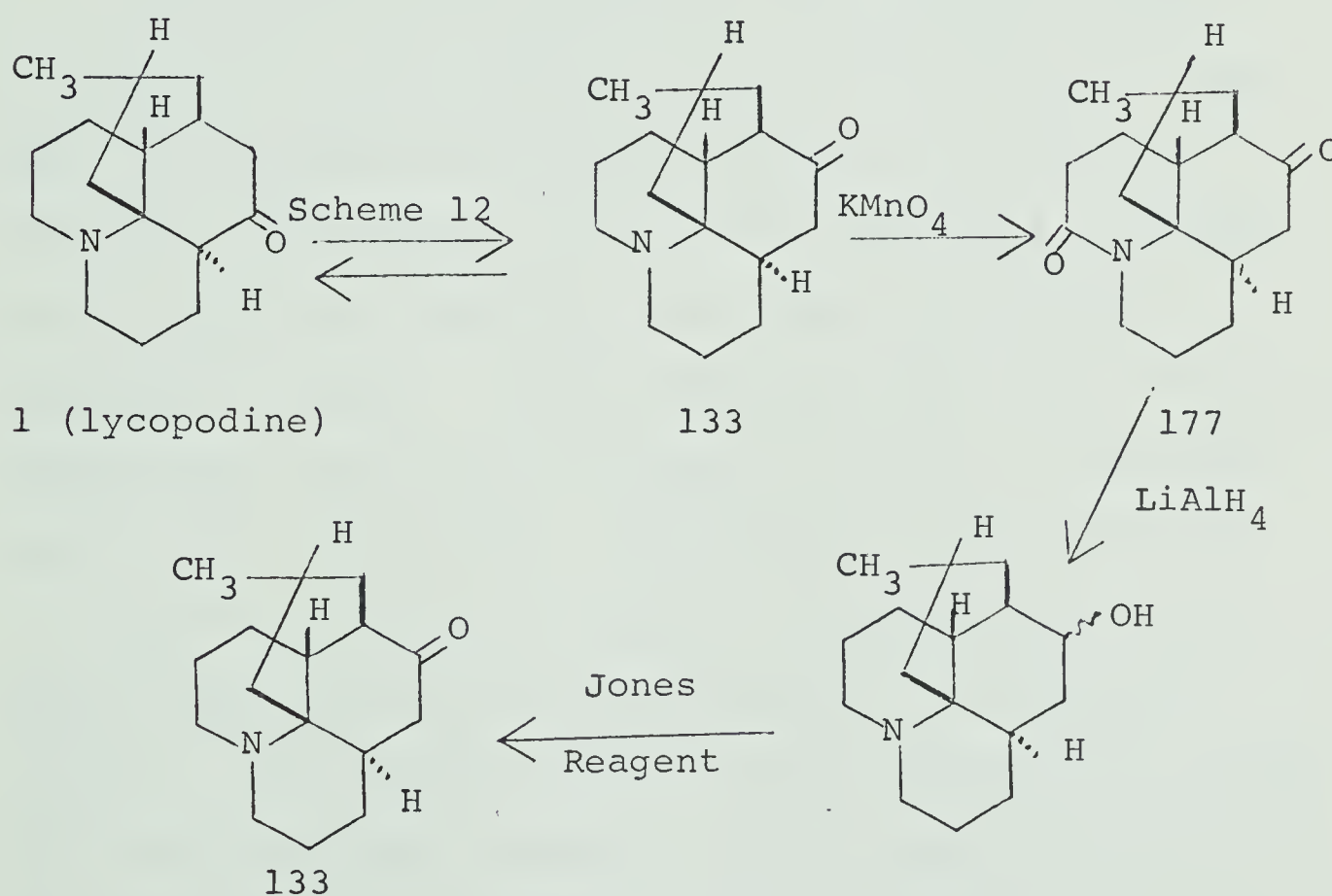
desired material, however, seemed so poor that this route was abandoned.



Scheme 24.



The next method investigated for blocking the nitrogen was the formation of the methiodide (scheme 24). Dr. T. C. Joseph in these laboratories prepared the methiodide of the relay compound 133 and found it could be reconverted to 133 by pyrolysis at 200°. The methiodide of alcohol 170 did not form at all readily. The impure methiodide of 170 was reacted as shown in scheme 24, but the results were not encouraging.



Scheme 25



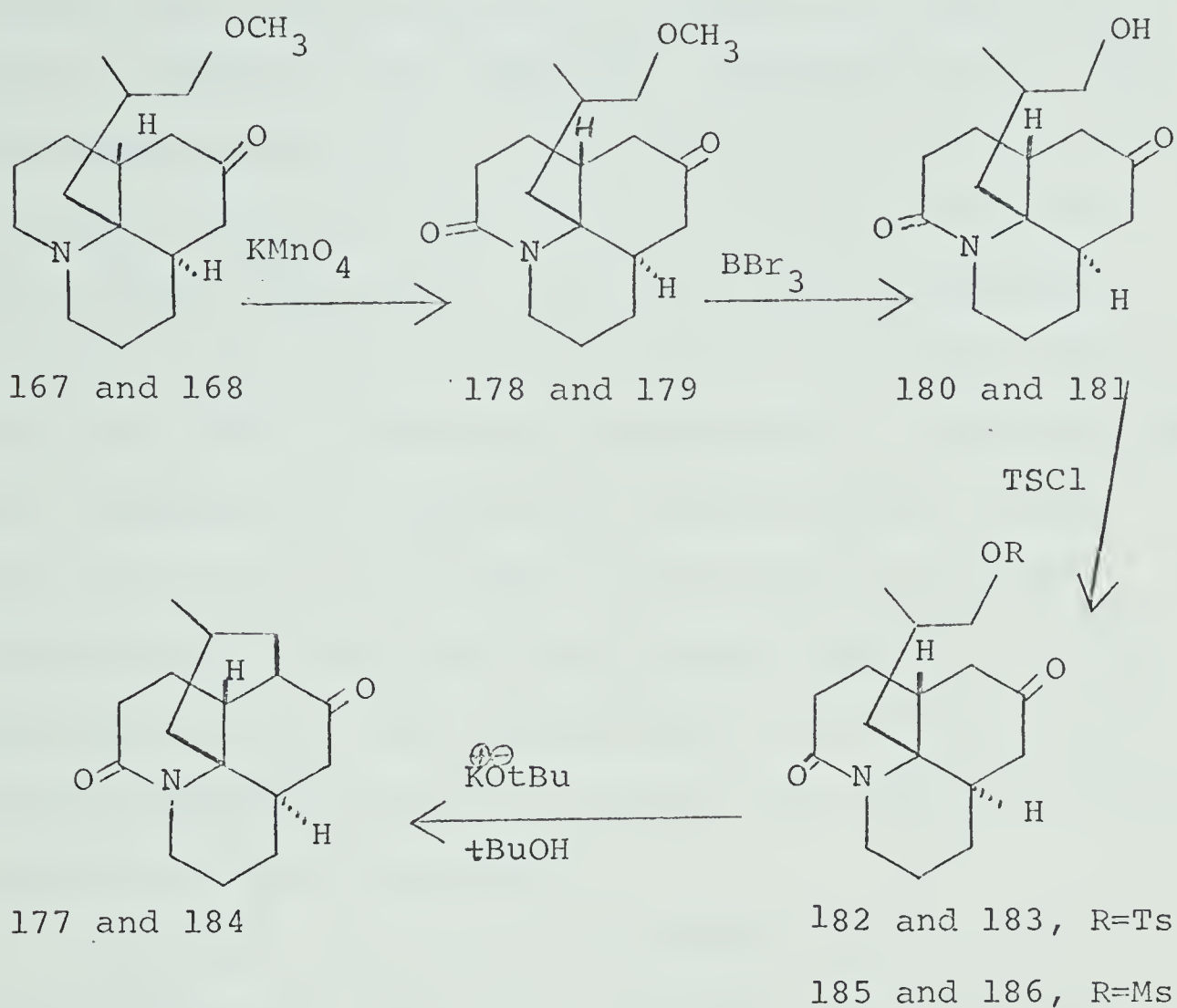


An attempt to make the N-methyl salt by the use of methyl p-toluenesulphonate was unsuccessful.

Lycopodine has been oxidised to its lactam by Ayer, Law, and Piers<sup>25</sup> in about 30% yield. This method of blocking the nitrogen had been avoided at first because of the low yield in the oxidation. Dr. T.C. Joseph prepared the lactam 177 from the compound 133 and then reconverted it to lycopodine as shown in scheme 25. The ring closed compound 133 had been prepared from lycopodine as shown previously in scheme 12.

The sequence contemplated at this point is shown in scheme 26. The methoxy ketones were oxidised<sup>25</sup> in about 20% yield to the mixture of methoxy lactams 178 and 179. The alcohols 169 and 170 could not be oxidised as they would be transformed into the corresponding aldehydes or acids. In the oxidation about 30% of starting material was isolated in the basic fraction. This basic portion was re-oxidised. The methoxy lactams 178 and 179 were not purified for further reactions but a small portion was purified by chromatography for characterisation. The infrared spectrum showed absorption at  $1650\text{ cm}^{-1}$  for the lactam carbonyl. The nmr spectrum showed the  $C_1$  equatorial hydrogen at  $\tau$  5.3 (d,  $J = 14$  cps). The hydrogen is deshielded<sup>25,81</sup> by the lactam carbonyl group.





Scheme 26

The methoxy lactams 178 and 179 were treated with boron tribromide in methylene chloride to give the lactam alcohols 180 and 181 in 70% yield (15% from the methoxy ketones 167 and 168). Although the lactam alcohols had slightly different  $R_F$  values they were too similar to allow easy chromatographic separation.

The mixture of the lactam alcohols 180 and 181 was



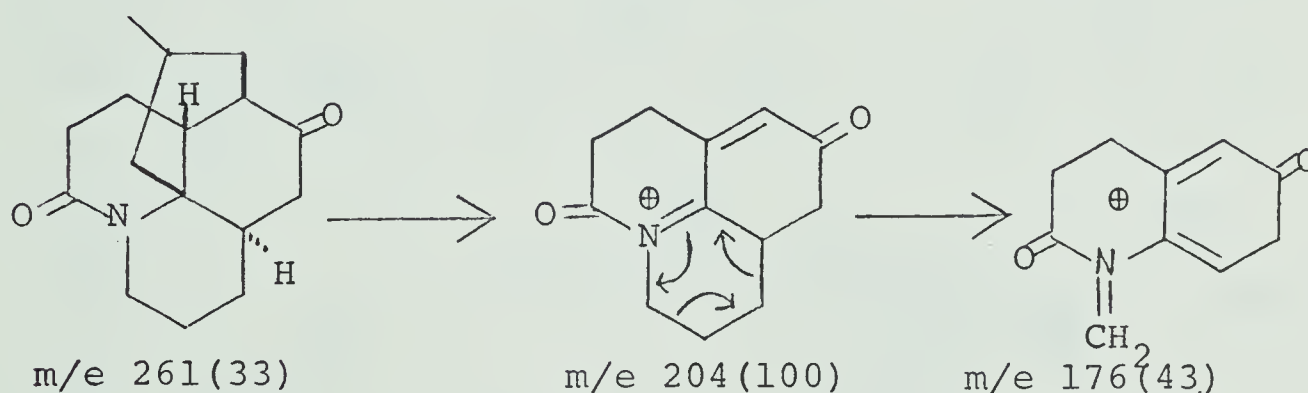
treated with p-toluenesulphonyl chloride in pyridine to give a mixture of two compounds. On separation by column chromatography the one was found to be the mixture of lactam tosylates 182 and 183 (tlc showed two spots with almost identical  $R_F$  values for the two diastereoisomers). The other compound was not positively identified; the infrared spectrum showed peaks at 1630 and 1720  $\text{cm}^{-1}$  indicating a lactam and a carbonyl group. The only major peak in the mass spectrum was at  $m/e$  206 indicating that the side chain is only joined the ring skeleton at  $C_{13}$ . This product may arise by elimination of the tosylate to form an olefin in the side chain, but was not further investigated.

Treatment of the lactam alcohols 180 and 181 with methanesulphonyl chloride in pyridine gave the desired product in high yield. The TLC showed two components with very similar  $R_F$  values indicating that both diastereoisomers were still present.

The mesyl lactams 185 and 186 were treated with potassium tertiary butoxide in tertiary butyl alcohol under nitrogen. A mixture of four products was obtained, one of which had the same  $R_F$  value as the lactam 177. The four components were separated by column chromatography. Three of these could not be definitely identified although the infrared and mass spectra were obtained. The data



pertaining to these compounds is tabulated in the experimental section. The fourth component had the same chromatographic behaviour as the lactam 177. The infrared and nmr spectra were similar but not identical. The nmr spectrum showed only a doublet for the C<sub>15</sub> methyl group ( $\tau$  8.97, J=6 cps) so it was not possible to judge whether or not both isomers 177 and 184 were present. Tlc showed only one spot, and not two with very similar R<sub>F</sub> values as is observed for the diastereoisomers of all the other compounds. The mass spectrum (scheme 27) was almost identical with that of the authentic lactam 177. The most likely conclusion is that both ring closed lactams 177 and 184 had been formed, and this was later shown to be true. Crystal-



Scheme 27

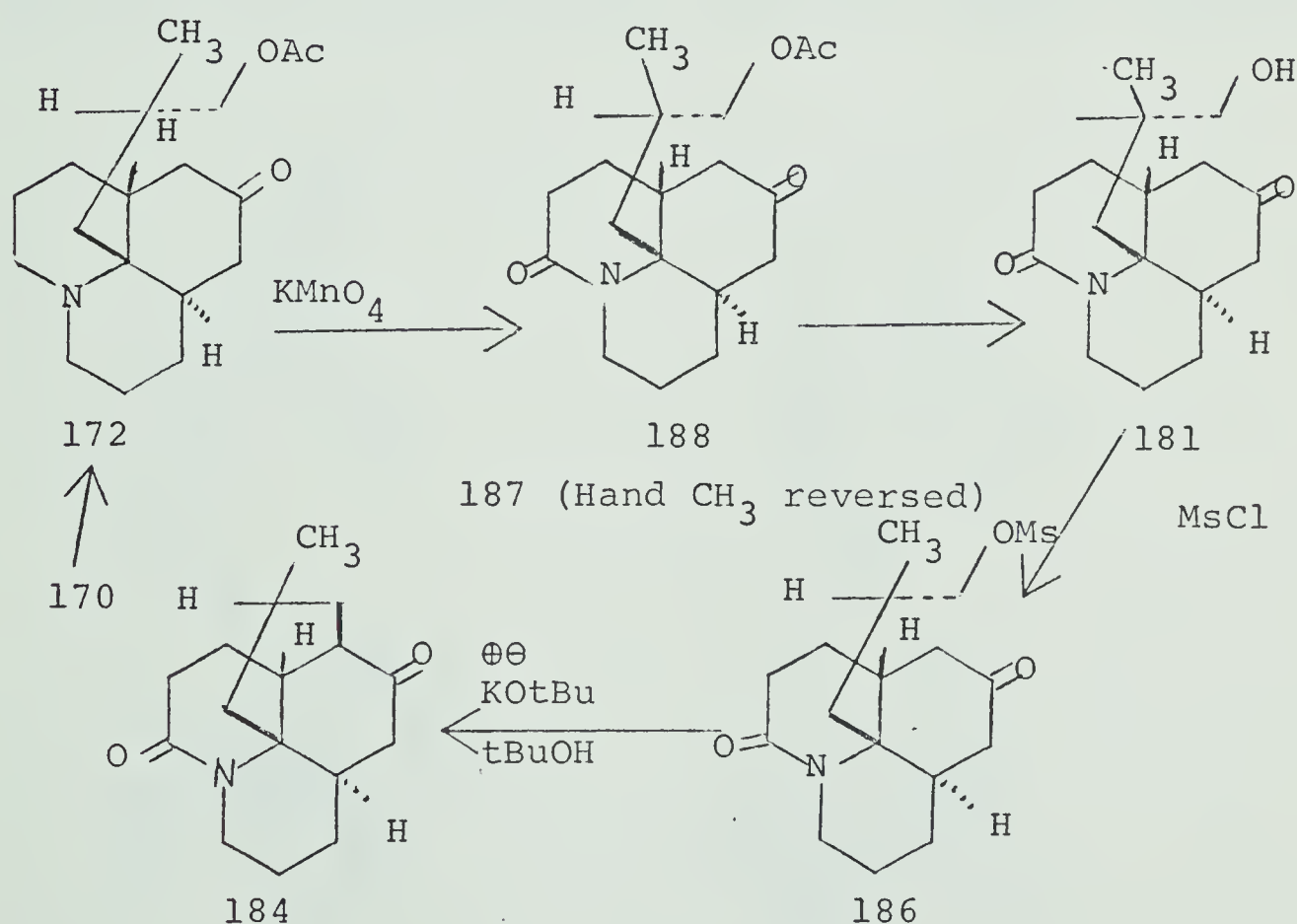
lisation gave colourless crystals with a sharp melting point of 151-152° which did not agree with that of 177 (142-143°). However, since we are dealing now with racemic material this was not too meaningful. The ir





spectrum in solution was different from that of 177. Since the mass spectrum was almost identical with that of 177, we felt that this was the C<sub>15</sub> epimer, 184.

The problem at this stage was to find a method to separate the diastereoisomers. Of the compounds investigated to this point only the alcohols 169 and 170 could be easily separated and they were not suitable for potassium permanganate oxidation. The acetates 171 and 172 had however been prepared and they should be stable to oxidation. Alcohol 170 was therefore treated as shown in scheme 28. Alcohol 170 was used first as it was the

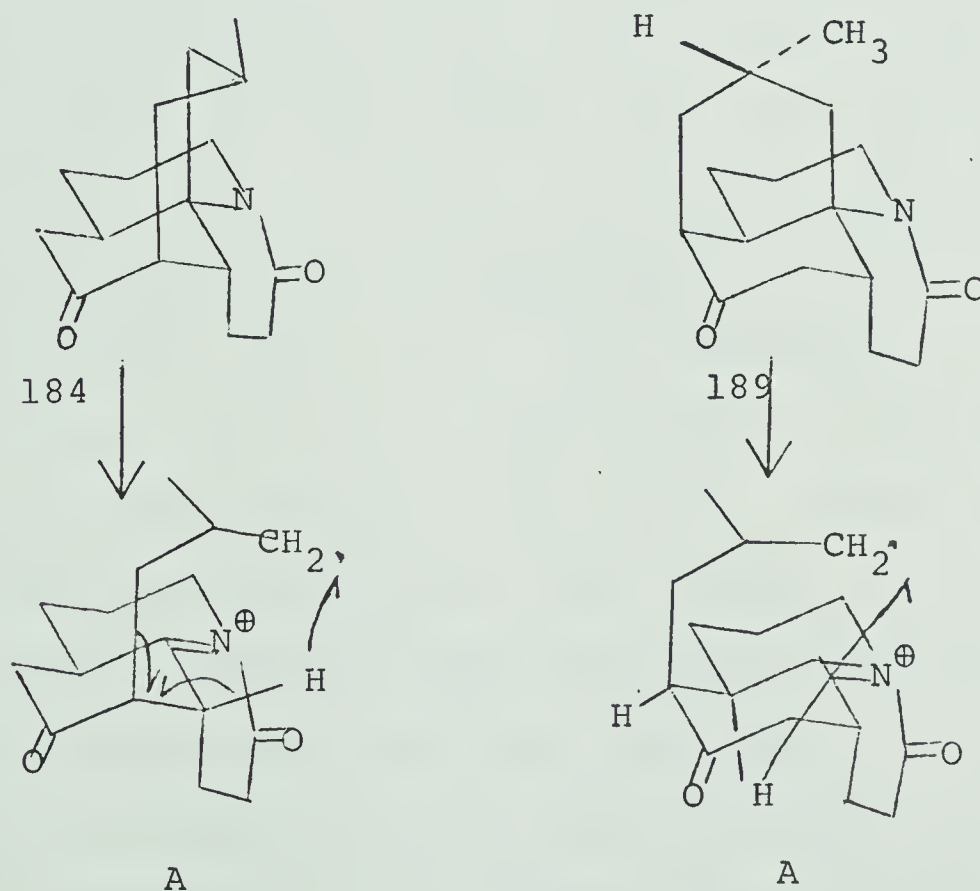


Scheme 28



alcohol separated in major proportions and until this sequence was finished its stereochemistry was not known.

The acetate 172 gave a mixture of the lactam acetate 188 and the lactam alcohol 181 on oxidation. The mixture was therefore hydrolysed without further purification to give the lactam alcohol 181. The lactam alcohol 181 was treated with methanesulphonyl chloride to give the mesylate. The mesylate 186 was then treated with potassium tertiary butoxide by the previously elaborated method to give a mixture of three compounds. They were separated by preparative tlc. The major product was the



Scheme 29



lactam 184, the stereochemistry of which was now apparent since it was not the same as the natural lactam 177. One of the other components was isomeric with 184 and is believed to result from ring closure on the opposite side of the carbonyl group. The structure of compound 189 was assigned on the basis of the mass spectrum as shown in scheme 29. In order for the side chain <sup>42</sup> to be eliminated readily from a fragment A the C<sub>4</sub> or C<sub>12</sub> hydrogen must shift to the radical as shown. In 184 this hydrogen is in a suitable position for intramolecular abstraction but in 189 it is not. Therefore the side chain should be eliminated more readily in 184 than in 189. The result should be a relatively more intense parent peak in 189 than in 184. The mass spectra show this to be the case (m/e 261(74) for 189 and m/e 261(42) for 184). The infrared spectrum showed absorption at 1625 cm<sup>-1</sup> for the lactam ketone and 1710 cm<sup>-1</sup> for the ketone.

Alcohol 169 was now assumed to have the right stereochemistry for the preparation of 177. It was treated under the same conditions as for alcohol 170 (scheme 28). Ring closure catalysed with potassium tertiary butoxide gave one major and two minor components (by tlc). Separation by preparative tlc showed the major component to be 177, identical in all aspects with the natural material except for the melting point. The melting point of the dl lactam



177 prepared was 157-158° while that of the optically pure natural material 177 was 142-143°. The mixed melting point was 153-154°. It is not uncommon for the dl racemate to melt higher than the d or l isomers.

This work represents the first synthesis of lycopodine (via the natural relay compound 177). The synthesis of lycopodine was also completed at this time by G. Stork, R. A. Kretchmer, and R. H. Schlessinger at Columbia University <sup>82</sup>. Thus 89 years after Bodeker's isolation of lycopodine and eight years after its structure was determined by Maclean, the synthesis of the major Lycopodium alkaloid has been achieved.

Current work in this laboratory is concerned with preparing the optically active Grignard reagent from optically active 1-chloro-2-methyl-3-methoxypropane. Therefore by using the same sequence of reactions the naturally occurring optical isomer of lycopodine can be prepared.





## Experimental

### Part 3

The general conditions for this section are the same as tabulated in Part 2.

#### The Synthesis of Lycopodine

##### The Preparation of 1,2,3,4-Tetrahydro-6-methoxyquinoline.

6-Methoxyquinoline (25 gms, 0.16 moles) was dissolved in glacial acetic acid (100 mls), to which was added 5% rhodium on alumina (2.5 gms). The resulting suspension was hydrogenated at 50 psi at room temperature in a Parr Hydrogenator. Hydrogen was taken up slowly over three days. The catalyst was removed by filtration and evaporation of the solvent yielded a black liquid. The liquid was taken up in ether and washed with saturated sodium bicarbonate solution. The ethereal extract was dried ( $\text{MgSO}_4$ ), concentrated, and distilled giving 1,2,3,4-tetrahydro-6-methoxyquinoline (16.0 gms, 62%): mp 100-105° (0.5 mm). The ir and nmr were identical with those of authentic material.

##### The Preparation of 9-methoxyjulolidine

1,2,3,4-Tetrahydro-6-methoxyquinoline (70 gms, 0.43 moles) was dissolved in 1-bromo-3-chloropropane (275 ml), and refluxed for 15 hours. After cooling the solution was acidified with 2N hydrochloric acid (200 ml) and



washed with ether (100 ml, two times). The aqueous portion was basified with conc. ammonium hydroxide and extracted with ether (100 ml, five times). The ethereal extract was dried ( $\text{MgSO}_4$ ), concentrated, and distilled to give 52 gms (50%) of 9-methoxyjulolidine: bp 125-135° (1.0 mm). The ir and nmr spectra were identical with those of authentic material.

#### The Methallyl Ketal 129.

Magnesium (3.0 gms, 0.12 moles) was placed in a one litre three necked flask with a reflux condenser, mechanical stirrer and a nitrogen inlet. The nitrogen was dried by passing it through a wash bottle of concentrated sulphuric acid. The apparatus was flame-dried and allowed to cool under anhydrous conditions. Tetrahydrofuran (200 ml), freshly distilled from lithium aluminum hydride, was added to the flask. Methallyl chloride (5.4 gms, 0.06 moles) in 200 ml dry tetrahydrofuran was added dropwise over three hours to the stirred solution under nitrogen. After this mixture was refluxed for ten hours, 9-ethylene-dioxy-8,9,10,10a-tetrahydrojulolidine perchlorate (10.0 gms, 0.03 moles) was added, and the suspension refluxed for a further three hours. The reaction mixture was filtered and the Grignard reagent destroyed by the addition of water (500 ml). The aqueous reaction mixture was



extracted with ether (100 ml, five times), dried ( $\text{MgSO}_4$ ), and evaporated to a yellow oil (7.0 gms). Tlc showed the presence of one major and three minor components in the oil.

This mixture was subjected to column chromatography on basic alumina and the progress of elution followed by tlc. Elution with Skellysolve B (1500 ml) yielded compound 130 (400 mg) as a colourless oil. Infrared ( $\text{CCl}_4$ ) 895, 1630, 3050  $\text{cm}^{-1}$  (C=C), 2670, 2755, 2800, 2500  $\text{cm}^{-1}$  (Bohlmann bands) and nmr (benzene)  $\tau$  5.10 (2H, d,  $J=9$  cps,  $=\text{CH}_2$ ) were identical with authentic material.

Further elution with Skellysolve B (4l) gave mixed fractions and then the methallyl ketal 129 (4.3 gms, 50%): mp 64.5-66°, ir ( $\text{CCl}_4$ ) 895, 1635, 3080  $\text{cm}^{-1}$  (C=C) and 2690, 2700, 2760, 2790, 2820  $\text{cm}^{-1}$  (Bohlmann bands); nmr (benzene)  $\tau$  5.1 (2H, broad,  $=\text{CH}_2$ ), 6.3 (4H, d,  $-\text{O}-\text{CH}_2-$ ). The spectra were identical with those of authentic material. Elution with benzene (2l) gave some mixed fractions. Further elution with benzene-ether (3:1 2l) gave compound 131 (500 mg): ir ( $\text{CCl}_4$ ) 2600, 2680, 2700, 2750, 2770, 2810,  $\text{cm}^{-1}$  (Bohlmann bands); nmr ( $\text{CCl}_4$ )  $\tau$  6.41 (4H, s,  $-\text{OCH}_2-$ ); hydroperchlorate (from ethyl acetate): mp 225-7°; ir (nujol) 3080  $\text{cm}^{-1}$  ( $\text{N}^{\oplus}\text{H}$ ). These data were identical with those of authentic material. The mass spectrum of the free base was taken as further evidence (200°, heated inlet) m/e



(rel. intensity) 247 (parent(32)), 246(100), 192(34), 146(12). Elution with ether (1ℓ) gave compound 132 (300 mg): ir ( $\text{CCl}_4$ ) 2600, 2685, 2760, 2810  $\text{cm}^{-1}$  (Bohlmann bands); nmr ( $\text{CDCl}_3$ )  $\tau$  6.05 (4H, s,  $-\text{OCH}_2-$ ); hydroperchlorate (from ethyl acetate: mp 260-262°; ir (nujol) 3060  $\text{cm}^{-1}$  ( $\text{N}^{\oplus}\text{H}$ )). The spectra were identical with authentic material. The mass spectrum (200°, heated inlet) m/e (rel. intensity) 247(30), 246(100), 192(33).

#### Photolysis of the Methallyl Ketal 129.

The methallyl ketal 129 (1 gm) was dissolved in pyridine (70 ml) and placed in a Pyrex tube (30 x 2½ cm). Oxygen was bubbled continuously through a sintered glass tube at the bottom of the solution. Hematoporphyrin (8 mg) was added to the solution. The tube was irradiated by four 18 inch fluorescent lamps for 1 week. Samples (5 ml) were removed at 40 hours, 90 hours and 1 week. Each sample was evaporated and the residue taken up in tetrahydrofuran. The colour was removed by Norite treatment. Lithium aluminum hydride (250 mg) was added and the slurry stirred for one hour. Water (0.25 ml) was added, the solution dried ( $\text{MgSO}_4$ ), and filtered. Evaporation of the solvent gave a crystalline solid which was identical with starting material (ir and tlc).





#### Treatment of the Methallyl Ketal 129 with N-Bromosuccinimide

The methallyl ketal 129 (400 mg) was dissolved in ether (25 ml) and conc. hydrobromic acid (48%) was added dropwise until the solution was acidic. A semi-crystalline gum separated. It was recrystallised from ethyl acetate. The hydrobromide (275 mg) was dissolved in chloroform (alcohol free, 15 ml). N-Bromosuccinimide (246 mg, 2 molar equiv.) and dibenzoyl peroxide (17 mg) were added with stirring. The solution was refluxed for 20 hours. The chloroform solution was extracted into 1N hydrochloric acid (50 ml), basified with saturated sodium bicarbonate solution and extracted into chloroform (50 ml, three times). The solution was dried ( $\text{MgSO}_4$ ) and concentrated to give a crystalline solid which was identical with starting material (ir and tlc).

#### Peracid Oxidation of the Methallyl Ketal

m-Chloroperbenzoic acid (350 mg, 1.5 mmoles based on 75% purity) was added in small portions over one half hour at  $0^\circ$  to the methallyl ketal 129 (400 mg, 1.35 mmoles) in chloroform (50 ml). The solution was stirred at  $0^\circ$  for eight hours and then at room temperature for 12 hours. It was diluted with chloroform (100 ml) and washed with sodium sulphite solution (10%, 75 ml, three times) and sodium bicarbonate (10%, 50 ml, three times). The chloroform solution was dried ( $\text{MgSO}_4$ ) and concentrated, giving brownish crystals. Recrystallisation



from ethyl acetate-ether yielded the N-oxide 139 (380 mg, 90%): mp 198-200°; ir (nujol and  $\text{CHCl}_3$ )  $957\text{ cm}^{-1}$  ( $\text{N}^{\oplus}-\text{O}^{\ominus}$ ); nmr ( $\text{CDCl}_3$ )  $\tau$  6.10 (4H, d,  $-\text{OCH}_2-$ ), 5.10 (2H, d,  $=\text{CH}_2$ ); mass spectrum (200°, heated inlet) m/e (rel. intensity) 236(100), 192(30). Anal. calcd for  $\text{C}_{18}\text{H}_{29}\text{NO}_3$ : C, 70.37; H, 9.44; N, 4.56. Found: C, 70.66; H, 9.64; N, 4.76.

The N-oxide 139 (200 mg) was reacted under identical conditions with m-chloroperbenzoic acid (350 mg). The material isolated was identical with starting material (ir and tlc). The reaction was repeated with the methallyl adduct hydroperchlorate (250 mg) and m-chloroperbenzoic acid (350 mg). The product was again identical with the N-oxide 139 (ir and tlc).

#### Treatment of the Methallyl Ketal 129 with Hypobromous Acid.

The hydroperchlorate was prepared by adding perchloric acid (70%): ethanol (1:1) dropwise to a solution of the methallyl ketal 129 in ether. Recrystallisation from ethyl acetate-methanol gave white crystals: mp 247-249°.

The hydroperchlorate (300 mg, 0.76 mmoles) and N-bromosuccinimide (200 mg, 2.1 mmoles) were added to water (20 ml) and stirred for 12 hours. The reaction was diluted with water (50 ml) and basified with potassium carbonate. The aqueous portion was extracted with chloroform (75 ml,



three times), dried ( $\text{MgSO}_4$ ), and evaporated to a gum (210 mg). Tlc indicated that the starting material had been consumed, but that a number of products had been obtained. These proved to be intractable.

The reaction was repeated on the free base (300 mg) in dioxan-water (30 ml 2:1) with N-bromosuccinimide (185 mg). Again the product was intractable.

#### The Hydroxy Ketal 140.

The methallyl ketal 129 (2.0 gms, 6.9 mmoles) was dissolved in tetrahydrofuran (50 ml, freshly distilled from lithium aluminum hydride). Diborane was generated by dropping sodium borohydride (2.0 gms) in diglyme (40 ml, dried by distillation from lithium aluminum hydride) into boron trifluoride-etherate in dry diglyme (5 ml) over one hour. The diborane was bubbled through the tetrahydrofuran solution in a stream of nitrogen with rapid stirring. The solution was stirred for 12 hours. The solution was cooled to  $0^\circ$  and ice carefully added. 3M sodium hydroxide (10 ml) and then 30% hydrogen peroxide (10 ml) were added dropwise with stirring at  $0^\circ$ . After stirring for 45 minutes at room temperature the solution was diluted with water (100 ml). The solution was extracted with chloroform (100 ml, five times), dried ( $\text{MgSO}_4$ ), and concentrated to yield a gummy product (2.3 gms). Tlc indicated that the



desired product was present in approximately 90% yield. A small portion was purified by column chromatography on alumina: ir ( $\text{CHCl}_3$ ) 2695, 2705, 2770, 2795, 2815  $\text{cm}^{-1}$  (Bohlmann bands), 3400, 3650  $\text{cm}^{-1}$  (OH); nmr ( $\text{CDCl}_3$ )  $\tau$  8.93 (3H, d,  $J=6$  cps,  $-\text{CH}-\text{CH}_3$ ), 6.55 (2H, d,  $J=6$  cps,  $\text{CH}_2\text{OH}$ ), 6.05 (4H, s,  $-\text{OCH}_2$ ).

The reaction when carried out with shorter reaction times gave differing yields of the product and starting material: 2 hours - approx. 20% product, 80% starting material;  $\frac{1}{2}$  hour - approx. 5% product, 95% starting material (estimated by ir and tlc).

The reaction when carried out with longer stirring time (16 hours) yielded 100% of a more polar product which also did not crystallise: ir ( $\text{CCl}_4$ ) 2670, 2740, 2765, 2800  $\text{cm}^{-1}$  (Bohlmann bands), 3450, 3580, 3620  $\text{cm}^{-1}$  (OH) nmr ( $\text{CDCl}_3$ )  $\tau$  8.95 (3H, d,  $J=6$  cps,  $\text{CH}-\text{CH}_3$ ), 6.3-6.6 (6H,  $-\text{OCH}_2$ ). Without further purification the product was acetylated in pyridine-acetic anhydride (10 ml and 10 ml) for 30 hours. The solvent was evaporated to 2.2 gms of gum. The gum was passed through an alumina column with benzene (1l) to remove more polar impurities to give 2.0 gms of a homogeneous gum (by tlc): ir ( $\text{CCl}_4$ ) 1250, 1740  $\text{cm}^{-1}$  (acetyl C=O); nmr ( $\text{CDCl}_3$ )  $\tau$  8.95 (2H, d,  $J=6$  cps,  $-\text{CH}-\text{CH}_3$ ), 6.30 (2H, t,  $J=5$  cps,  $-\text{OCH}_2\text{CH}_2$ ) 6.10 (2H, d,  $J=5$  cps,  $-\text{CH}(\text{CH}_3)\text{CH}_2\text{OAc}$ ), 5.77 (2H, t,  $J=5$  cps,  $-\text{CH}_2\text{CH}_2\text{OAc}$ ), 7.91







(6H, s,  $-\text{OCOCH}_3$ ) mass spectrum ( $200^\circ$ , heated inlet) m/e (rel. intensity) 395(1), 280(100), 176(11), 150(32).

#### The Hydroxyketone 142.

The crude hydroxylation product (2.3 gms from 2.0 gms) was stirred in methanol (60 ml), water (220 ml) and conc. hydrochloric acid (60 ml) for 24 hours. At the end of this period the reaction was basified with granular sodium carbonate and extracted with chloroform (100 ml, five times), dried ( $\text{MgSO}_4$ ), and concentrated to a non-crystalline gum (1.74 gms, 85% from methallyl ketal 129): hydroperchlorate, mp  $245-7^\circ$ ; Anal. Calcd for  $\text{C}_{16}\text{H}_{27}\text{NO}_2 \cdot \text{HClO}_4$ : C, 52.64; H, 7.73; N, 3.84. Found: C, 52.71; H, 7.80; N, 3.98; Free base: ir ( $\text{CHCl}_3$ )  $1712\text{ cm}^{-1}$  (C=O)  $2700, 2795, 2825\text{ cm}^{-1}$  (Bohlmann bands),  $3470, 3650\text{ cm}^{-1}$  (OH); nmr ( $\text{CDCl}_3$ )  $\tau$  9.0 (3H, d,  $J=5.5$  cps,  $-\text{CH}-\text{CH}_3$ ), 6.55 (2H, d,  $J=5.5$  cps,  $-\text{CH}_2\text{OH}$ ); mass spectrum ( $200^\circ$ , heated inlet) m/e (rel. intensity) 247(13), 192(100).

#### The Hydroxy Bromoketone 146.

The hydroxyketone 142 (400 mg, 1.5 moles) was dissolved in methanol (40 ml) and conc. hydrobromic acid (48%) was added dropwise until the solution was acidic. A non-crystalline froth was obtained on evaporation. The hydrobromide was dissolved in chloroform (25 ml), to which bromine (240 mg, 1.5 moles) in chloroform (25 ml) was added drop-wise with stirring at such a rate that the red bromine colour did not



persist. A non-crystalline froth (640 mg) was obtained on evaporation: ir ( $\text{CHCl}_3$ )  $1736\text{ cm}^{-1}$  ( $\text{C=O}$ ); nmr (deuteroacetone)  $\tau$  8.95 (3H, d,  $J=6.5$  cps,  $\text{CH-CH}_3$ ), 3.75 (1H, d,  $J=13$  cps,  $-\text{CH}(\text{Br})$ ). The free base decomposed instantly when liberated.

#### Dehydrobromination using Lithium Bromide.

The hydroxy bromoketone hydrobromide 146 (200 mg, 0.5 mmoles), lithium bromide (200 mg, 2 mmoles), and lithium carbonate (300 mg) were heated under nitrogen in dimethylformamide (15 ml, dried by distillation from anhyd. barium carbonate) for 20 hours at  $95^\circ$ . Water (50 ml) was added and extracted with chloroform (50 ml, three times), dried ( $\text{MgSO}_4$ ), and evaporated to a gum (130 mg). There were no recognisable products (no major spot on tlc or  $\alpha,\beta$ -unsat. ketone absorption in the ir). The reaction was repeated with 3 hours heating but with similar results.

#### Treatment of the Hydroxy Bromoketone Hydrobromide 146 with 2,4-Dinitrophenylhydrazine.

The hydroxy bromoketone hydrobromide 146 (100 mg, 0.24 mmoles) was dissolved in glacial acetic acid (5 ml) under nitrogen. 2,4-Dinitrophenylhydrazine (50 mg, 0.30 mmoles) dissolved in glacial acetic acid (5 ml) was added to the refluxing solution. The mixture was refluxed for one hour, cooled, and diluted with water (50 ml). No crystals or precipitate formed on cooling. After basifi-



cation with conc. ammonium hydroxide, red crystals formed. The crystals were filtered from the solution (44 mg). Extraction of the aqueous solution with chloroform did not yield any more product. The crystals were purified by column chromatography on alumina. Elution with benzene (100 ml) gave homogeneous (tlc) material (40 mg, 35%): mp (from 95% ethanol) 196-198°; uv max (95% ethanol) 388 mμ (expected ca. 380 mμ); ir (CCl<sub>4</sub>) 1590, 1610 cm<sup>-1</sup> (C=CH-C=N, and aromatic), 1720 cm<sup>-1</sup> (acetyl), 3015 cm<sup>-1</sup> (C=C), 3100 cm<sup>-1</sup> (aromatic), 3300 cm<sup>-1</sup> (NH); nmr (CDCl<sub>3</sub>) τ 7.8 (q, CH-CH<sub>3</sub>), 7.9 (d, OAc), 6.0 (g, CH<sub>2</sub>-OAc), 3.8 (t, C=C(H)-C=N), 1.19(A), 1.65(B) 2.00(C) (J<sub>AB</sub>=2.5 cps), J<sub>BC</sub>=9.5 cps, aromatic), -1.02 (s, NH); Anal. Calcd for C<sub>24</sub>H<sub>31</sub>N<sub>5</sub>O<sub>6</sub>: C, 59.39; H, 6.44; N, 13.58. Found: C, 58.78; H, 6.28; N, 13.58. (The analysis is not satisfactory but no more compound was available).

#### The Acetoxy Ketone 155.

The hydroxyketone 142 (500 mg, 1.9 mmoles) was stirred in pyridine (7 ml, dried over potassium hydroxide) and acetic anhydride (7 ml). Water (100 ml) was added and the solution basified with conc. ammonium hydroxide. The basic solution was extracted with ether (75 ml, three times), dried (MgSO<sub>4</sub>), and evaporated to a non-crystalline gum (480 mg, 90%): hydroperchlorate; mp 205-206°, Anal. Calcd for



$C_{18}H_{29}NO_3$ : C, 53.01; H, 7.41; N, 3.43. Found: C, 53.12; H, 7.33; N, 3.02; free base: ir ( $CCl_4$ )  $1225, 1735\text{ cm}^{-1}$  (acetate),  $1715\text{ cm}^{-1}$  (C=O) nmr ( $CDCl_3$ )  $\tau$  9.0 (3H, d,  $J=6$  cps,  $CH-CH_3$ ), 7.93 (3H, s,  $OCOCH_3$ ), 6.10 (2H, d,  $J=6$  cps,  $CH_2-OAc$ ).

#### The Acetoxy Bromoketone 156.

The acetoxyketone 155 (500 mg, 1.5 mmoles) was dissolved in methanol (50 ml). Conc. hydrobromic acid (48%) was added dropwise until the solution was acidic. The solvent was evaporated to yield a colourless froth: ir ( $CHCl_3$ )  $1722\text{ cm}^{-1}$  (C=O),  $2600\text{ cm}^{-1}$  ( $N^{\oplus}H$ ). The salt was dissolved in chloroform (25 ml) to which bromine (260 mg, 1.6 mmoles) in chloroform (25 ml) was added at such a rate that the red bromine colour did not persist in the solution. A non-crystalline light brown froth was obtained on evaporation (777 mg): ir ( $CHCl_3$ )  $1740\text{ cm}^{-1}$  (C=O),  $2600\text{ cm}^{-1}$  ( $N^{\oplus}H$ ); nmr ( $CDCl_3$ )  $\tau$  8.85 (3H, d,  $J=5.5$  cps,  $CH-CH_3$ ), 7.90 (3H, s,  $OCOCH_3$ ), 6.05 (2H, d,  $J=5.5$  cps,  $CH_2OAc$ ); 4.0 (1H, d,  $J=12$  cps, (CH-Br)).

#### Treatment of the Acetoxy Bromoketone Hydrobromide 156 with 2,4-Dinitrophenylhydrazine.

The acetoxy bromoketone hydrobromide 156 (100 mg, 2.1 mmoles) was dissolved in glacial acetic acid (5 ml) under nitrogen. 2,4-Dinitrophenylhydrazine (47 mg, 2.4 mmoles) in







glacial acetic acid (5 ml) was added to the refluxing solution. The heating was continued for five minutes and then the solution was diluted with water (50 ml). The solution was basified with conc. ammonium hydroxide and filtered to give red crystals. The product was purified by chromatography on alumina. Elution with benzene (500 ml) gave the acetoxy  $\alpha,\beta$ -unsaturated 2,4-dinitrophenylhydrazone (52 mg, 50%). The product was identical to that prepared from the hydroxy compound (by tlc, uv, ir and nmr).

Hydrolysis of the Acetoxy  $\alpha,\beta$ -Unsaturated 2,4-Dinitrophenylhydrazone 154.

A. Acetone-hydrochloric acid.

The 2,4-dinitrophenylhydrazone 154 (80 mg) was dissolved in acetone (20 ml). Conc. hydrochloric acid (0.5 ml) was added and the solution refluxed under nitrogen for 2½ hours. The colour changed from red to yellow in five minutes. The uv maximum in acetone changed from 388 m $\mu$  to 365 m $\mu$  (acetone-2,4-dinitrophenylhydrazone: uv max (acetone) 365 m $\mu$ ). The solution was concentrated to 5 ml and water added (50 ml). Extraction with ether (50 ml, five times) dried (MgSO<sub>4</sub>), and evaporated to yellow crystals of the acetone-2,4-dinitrophenylhydrazone: (32 mg, 84%): mp 126-127° (reported 128°); ir and tlc identical to authentic



material. The aqueous portion was basified with potassium carbonate and extracted with ether (50 ml, five times), dried ( $\text{MgSO}_4$ ), and evaporated to 51 mg of gum. Tlc indicated no major component and ir showed no absorption due to an  $\alpha,\beta$ -unsaturated ketone.

#### B. Pyruvic acid.

The 2,4-dinitrophenylhydrazone 154 was dissolved in chloroform (5 ml, ethanol free). 84% Pyruvic acid (7.5 ml) and 30% hydrobromic acid (1.0 ml) were added. The mixture was sealed under nitrogen and heated at  $60^\circ$  for three hours with frequent shaking. The solution was poured into water (100 ml) basified with potassium carbonate and extracted with ether (50 ml, five times). On drying ( $\text{MgSO}_4$ ) and evaporation a brown gum was obtained. Tlc showed no major component or starting material and the ir showed no absorption due to an  $\alpha,\beta$ -unsaturated ketone.

#### Treatment of the Acetyl Bromoketone Hydrobromide 156 with Semicarbazide.

##### The preparation of a sample compound.

Methyl vinyl ketone (1.0 gm) was added to a solution of semicarbazide hydrochloride (1.0 gm) and anhydrous sodium acetate (1.5 gm) in water (9 ml). The solution was shaken, cooled, and filtered to give white crystals: mp (from 95% ethanol)  $139-140^\circ$  (reported  $141^\circ$ ); uv max (ethanol) 260 m $\mu$ ; ir ( $\text{CHCl}_3$ )  $1560\text{ cm}^{-1}$  (C=N),  $1630\text{ cm}^{-1}$  (C=C),  $1700\text{ cm}^{-1}$



(C=O); nmr ( $\text{CDCl}_3$ )  $\tau$  4.20 (broad,  $\text{NH}_2$ ), 3.5 (q,  $\text{C}=\text{C}(\text{H})\text{P}$ ), -1.0 (broad, NH).

#### Method 1.

The acetyl bromoketone hydrobromide 156 (150 mg, 0.32 mmoles) was dissolved in chloroform (6 ml, ethanol free) and tertiary butyl alcohol (9 ml), and flushed with carbon dioxide. Semicarbazide (56 mg, 0.75 mmoles, recrystallised from 95% ethanol) was added and again flushed with carbon dioxide and shaken mechanically for eight hours. After this time it was diluted with water (50 ml) basified with dilute ammonium hydroxide (70%) and extracted with chloroform (50 ml, seven times). After drying ( $\text{MgSO}_4$ ) the solution was evaporated to give a glassy compound (90 mg) which showed two spots on tlc in 2% methanol-chloroform. The two compounds were separated on alumina. On elution with chloroform (100 ml) a pure (by tlc) fraction was obtained: the acetoxy  $\alpha,\beta$ -unsaturated semicarbazone 157 (30 mg, non-crystalline glass). Further elution with chloroform (100 ml) gave a mixed fraction (10 mg), and yet further elution (100 ml) a second homogeneous component (by tlc) - the presumed saturated semicarbazone 158 (4 mg). Neither compound could be crystallised.

The saturated semicarbazone 158; uv max (95% ethanol) 230 m $\mu$  (reported for saturated semicarbazones 229 m $\mu$ ) ir ( $\text{CHCl}_3$ ) 1075  $\text{cm}^{-1}$  (-O-), 1550  $\text{cm}^{-1}$  (C=N), 1680  $\text{cm}^{-1}$  (C=O),



3400-3600  $\text{cm}^{-1}$  (NH and  $\text{NH}_2$ ).

The  $\alpha,\beta$ -unsaturated semicarbazone 157; uv max (95% ethanol) 275 m $\mu$  (reported for  $\alpha,\beta$ -unsaturated semicarbazones; 265 m $\mu$ ); ir ( $\text{CHCl}_3$ ) 1565  $\text{cm}^{-1}$  (C=N), 1695  $\text{cm}^{-1}$  (C=O), 1730  $\text{cm}^{-1}$  (acetyl C=O), 3400-3600  $\text{cm}^{-1}$  (NH and  $\text{NH}_2$ ); nmr ( $\text{CDCl}_3$ )  $\tau$  9.0 (3H, t (2d), CH-CH<sub>3</sub>) 8.0 (3H, s, OAc); 7.3 (2H, m,  $\text{CH}_2$ -C=N), 6.2 (2H, d,  $\text{CH}_2$ OAc), 4.31 (2H, broad s, disappears on  $\text{D}_2\text{O}$  exchange,  $\text{NH}_2$ ) 4.18 (1H, broad s, C=CH), 1.2 (1H broad, NH).

Neither compound gave a useful mass spectrum using the heated inlet but a mixture of the two was examined using the direct probe. The spectrum showed a base peak at m/e 247(100) and the two parent peaks at m/e 364(1) and m/e 320(5).

On using the same conditions with glacial acetic acid and ethanol free chloroform as solvent, no semicarbazone was obtained.

#### Method 2.

The acetoxy bromoketone hydrobromide 156 (150 mg) was dissolved in glacial acetic acid (5 ml) and heated to reflux under carbon dioxide. Semicarbazide (43 mg) was added and the solution was refluxed for 15 minutes under carbon dioxide. At the end of this period the reaction mixture was diluted with water (75 ml), basified with ammonium







hydroxide (10%) and extracted with chloroform (75 ml, five times). The chloroform solution was dried ( $\text{MgSO}_4$ ) and evaporated to a colourless glass (95 mg). Tlc showed two spots with very similar  $R_F$  values as before. The ir was identical with that of the product from Method 1.

The Acetoxy  $\alpha,\beta$ -Unsaturated Ketone 159.

The acetoxy bromoketone hydrobromide 156 (1015 mg, 2.2 mmoles) and semicarbazide (328 mg, 4.4 mmoles) were dissolved in glacial acetic acid (20 ml) and heated to reflux under carbon dioxide. The refluxing was continued for ten minutes under carbon dioxide. At the end of this time pyruvic acid (2.2 ml) and water (1.7 ml) were added and the refluxing continued for twenty minutes. The solution was cooled, diluted with water (250 ml), and basified with ammonium hydroxide (10%) under nitrogen. Extraction with ether (100 ml, five times), drying ( $\text{MgSO}_4$ ), and evaporation yielded a light yellow oil (470 mg). The oil was purified by column chromatography with alumina. Elution with ether:chloroform (9:1, 50 ml) gave a colourless oil (340 mg). Further elution with chloroform (50 ml) gave mixed fractions and then another 100 ml gave a mixture of two polar compounds with hydroxyl absorption in the ir. Fraction 1 showed 2 spots on the TLC with almost identical  $R_F$  values. These two compounds could not be separated by



further chromatography. Further experiments (see basic hydrolysis of the mixture) showed the components to be the acetoxy  $\alpha,\beta$ -unsaturated ketones and a ring closed ether.

The  $\alpha,\beta$ -unsaturated ketones 159 and 160; uv max (95% ethanol) 244 m $\mu$  (calculated 244 m $\mu$ ); ir (CCl<sub>4</sub>) 1665 cm<sup>-1</sup> (C=O), 1220, 1735 cm<sup>-1</sup> (OAc), 1615, 3020 cm<sup>-1</sup> (C=C), no Bohlmann bands; nmr (CDCl<sub>3</sub>, mixed with the ring closed ether)  $\tau$  9.17 (d, CH-CH<sub>3</sub> "ether"),  $\tau$  8.95 (t(2d)CH-CH<sub>3</sub>), 7.94 (d(2s), OAc), 6.09 (q(2d), J=6 cps, CH<sub>2</sub>OAc), 4.09 (d, (2s), C=CH); mass spectrum (190° heated inlet); m/e (rel. intensity) 305(1, parent) 263(3, parent), 245(5, loss of acetic acid), 192(38, base peak for " $\alpha,\beta$ -unsat"), 190 (45, base peak for "ether"), 150(100).

An experiment under identical conditions using the hydroxybromoketone hydrobromide 142 gave the same products in much lower yield.

#### Basic Hydrolysis of Dehydrobromination Products.

The dehydrobromination product (100 mg) was refluxed in 4% methanolic potassium hydroxide (25 ml) for 3 hours. Most of the methanol was removed and the residue dissolved in water (50 ml). Extraction with chloroform (50 ml, five times), drying (MgSO<sub>4</sub>), and evaporation gave a homogeneous product (77 mg). Tlc indicated only one compound with an



$R_F$  value identical with one of the starting materials, and no more polar material. It was purified by column chromatography on basic alumina. Elution with ether (50 ml) gave a white crystalline solid (60 mg): uv max - none; ir ( $\text{CCl}_4$ )  $1075\text{ cm}^{-1}$  (-O-),  $1715\text{ cm}^{-1}$  (C=O), 2680, 2760,  $2805\text{ cm}^{-1}$  (Bohlmann bands); nmr ( $\text{CDCl}_3$ )  $\tau$  9.15 (3H, d,  $J=6$  cps,  $\text{CH}-\text{CH}_3$ ); mass spectrum ( $160^\circ$  direct probe), m/e (rel. intensity) 263(38, mass = 263.1886 calcd = 263.1885 for  $\text{C}_{16}\text{H}_{25}\text{NO}_2$ ), 190(100), 163(48), 162(30).

Cleavage of the Ring Closed Ether 160.

A. Hydrochloric Acid. The ring closed ether 160 (50 mg) was refluxed for eight hours in 5% hydrochloric acid (20 ml). The solution was basified with potassium carbonate and extracted with chloroform (25 ml, three times). The extract was dried ( $\text{MgSO}_4$ ) and evaporated to 46 mg of crystalline starting material (by ir and tlc).

B. Boron trifluoride. The ring closed ether 160 (45 mg) was dissolved in ether (15 ml) and benzene (1 ml). Acetic anhydride (2 ml) and boron trifluoride-etherate (2 ml) were added dropwise to the stirred solution. The stirring was continued for 48 hours. Ether (50 ml) was added and the solution shaken with ammonium hydroxide (25 ml, 10%) for five minutes, separated, and the aqueous layer extracted with chloroform (25 ml, five times). The chloro-



form solution was dried ( $\text{MgSO}_4$ ) and evaporated to a viscous oil (66 mg). Tlc showed two spots, one corresponding to the acetoxy  $\alpha,\beta$ -unsaturated ketone 159, and a less polar component. They were separated by column chromatography on alumina. Elution with benzene (25 ml) gave the enol acetate 161 (26 mg); uv max (95% ethanol) 236 m $\mu$  (calculated 237 m $\mu$ ); ir ( $\text{CCl}_4$ ) 1620, 1665  $\text{cm}^{-1}$  (C=C), 1210, 1235, 1740, 1765  $\text{cm}^{-1}$  (OAc); nmr ( $\text{CDCl}_3$ )  $\tau$  8.93 (3H, d,  $J=6.5$  cps,  $\text{CH}-\text{CH}_3$ ), 7.97 (3H, s,  $\text{C}=\text{C}-\text{OAc}$ ), 4.48, 4.36 (broad s, d,  $\text{C}=\text{CH}$ ); mass spectrum (200°, heated inlet) m/e (rel. intensity) 347(1), 287(4), 232(100), 190(21). From this information it was assumed that the structure was that of an acetoxy dienol acetate.

Further elution with benzene (50 ml) gave a mixed fraction. Elution with ether (50 ml) gave 6.0 mg of the non-crystalline acetoxy  $\alpha,\beta$ -unsaturated ketone 159 (by ir and tlc).

#### Lithium - Ammonia Reduction of the Dehydrobromination Product.

The dehydrobromination product (100 mg) in ether (25 ml) was added to a solution of lithium (200 mg) in re-distilled liquid ammonia (150 ml) and stirred for thirty minutes. Anhydrous ammonium chloride was added until the blue colour disappeared. The dry ice-acetone condenser was then removed and the ammonia allowed to evaporate.







Water (100 ml) was added to the residue, and the solution extracted with chloroform (50 ml, five times). A viscous gum (93 mg) was obtained on drying ( $\text{MgSO}_4$ ) and evaporation of the chloroform extracts. Tlc indicated no major component and about ten minor components. Extensive chromatography did not lead to any recognisable product.

Repeated experiments with smaller quantities of lithium and shorter reaction times all led to the same products (by tlc).

#### Methyl 2-methyl-3-methoxypropionate <sup>75</sup>

Methyl methacrylate (200 gms, 2.0 moles) was refluxed with a solution of sodium (3 gms) in methanol (800 ml, distilled from magnesium) for 30 minutes. Most of the methanol was distilled off and the residue dissolved in ether (400 ml). The ethereal solution was washed with hydrochloric acid (10%, 100 ml, twice) and sodium hydroxide solution (10%, once) and then water. The extract was dried ( $\text{MgSO}_4$ ), concentrated, and distilled. Fraction 1,  $95^\circ$ , methyl methacrylate; fraction 2,  $140-147^\circ$ , product (61 gms, 21%). Ir and nmr confirmed the structure.

#### 2-Methyl-3-methoxypropanol.

Methyl 2-methyl-3-methoxypropionate (52 gms, 0.39 moles) in ether (300 ml) was added over two hours with rapid stirring to a suspension of lithium aluminum hydride



(11 g) in ether (350 ml). The suspension was refluxed for two hours and stirred for another twelve. The excess hydride was destroyed by adding dropwise, water (11 ml) and then 10% sodium hydroxide solution (11 ml). The solution was filtered, concentrated, and fractionated. The product boiling between 151° and 154° was taken (32 gms, 80%). The identity was confirmed by ir and nmr.

1-Chloro-2-methyl-3-methoxypropane<sup>76</sup>

2-Methyl-3-methoxypropanol (72 gms, 0.69 moles) and pyridine (55 gms, 0.70 moles) were cooled to 0°. Thionyl chloride (100 gms) was added dropwise at such a rate that the temperature did not exceed 60°. The solution was refluxed at 65° for three hours and then poured onto ice (140 gms) and conc. hydrochloric acid (35 ml). The aqueous solution was extracted with ether (100 ml, three times), dried ( $\text{MgSO}_4$ ), evaporated, and fractionated. Material boiling between 121° and 124° was taken (75 gms, 0.61 moles, 89%). The structure was confirmed by ir and nmr.

The Methoxy Ketal 163

A. (With very pure 9-ethylenedioxy-8,9,10,10a-tetrahydro-julolidine perchlorate). The perchlorate was slurried in hot methanol and filtered until the filtrate was colourless (five times).

Magnesium (6.0, 0.49 moles) was placed in a dried one



litre flask. Ether (350 ml) and then 1-chloro-2-methyl-3-methoxypropane (55 gms, 0.45 moles) and a crystal of iodine were added. After half an hour the solution became cloudy. It was then stirred and refluxed for two hours. Tetrahydrofuran (400 ml, freshly distilled from lithium aluminum hydride) was added and the ether removed by distillation. The solution was cooled and 9-ethylenedioxy-8,9,10,10a-tetrahydrojulolidine perchlorate (55 gms) added. The suspension was stirred and refluxed for one hour. The perchlorate rapidly dissolved. The solution was filtered and water (500 ml) added. The aqueous solution was extracted with ether (300 ml, three times), dried ( $\text{MgSO}_4$ ), and evaporated to a yellow oil (48 gms, 90%) which crystallised on standing. Tlc showed one component; mp 48-51°; ir ( $\text{CCl}_4$ ) 1080-1100  $\text{cm}^{-1}$  (ketal ether), 2760, 2805  $\text{cm}^{-1}$  (Bohlmann bands); nmr ( $\text{CDCl}_3$ )  $\tau$  8.95 (3H, d,  $J=6$  cps,  $\text{CH}-\underline{\text{CH}_3}$ ). 6.82 (2H, d,  $J=6$  cps,  $\text{CH}_2\text{OMe}$ ), 6.70 (3H, s,  $\text{OCH}_3$ ), 6.07 (4H, s,  $-\text{OCH}_2$ ); mass spectrum (180°, heated inlet) m/e (rel. intensity) 323(1), 236(100).  
Anal. Calcd for  $\text{C}_{19}\text{H}_{33}\text{NO}_3$ : C, 70.53; H, 10.28; N, 4.33;  
Found: C, 70.73; H, 10.20; N, 4.28.

B. With impure 9-ethylenedioxy-8,9,10,10a-tetrahydrojulolidine.

The above reaction was repeated using 1-chloro-2-methyl-3-methoxypropane (20.5 gms, 0.17 moles), magnesium



(4.5 gms, 0.37 moles) and impure 9-ethylenedioxy-8,9,10,10a-tetrahydrojulolidine (18 gms, 0.05 moles) and a three hour reaction time. A product (17.2 gms) containing three compounds (by tlc) was obtained. The components were separated by column chromatography on alumina. Elution with Skellysolve B (1250 ml) gave a colourless viscous liquid (1.5 gms): ir ( $\text{CCl}_4$ )  $1110\text{ cm}^{-1}$  ( $\text{OCH}_3$ ), 2760, 2800,  $2820\text{ cm}^{-1}$  (Bohlmann bands); nmr ( $\text{CDCl}_3$ )  $\tau$  8.95 (3H, d,  $J=6$  cps,  $\text{CH}-\text{CH}_3$ ), 6.80 (4H, m,  $-\text{OCH}_2$ ); 6.70 (3H, s,  $-\text{OCH}_3$ ); mass spectrum ( $180^\circ$  heated inlet) m/e (rel. intensity) 265(1), 178(100), 150(10).

Further elution with Skellysolve B (1250 ml) gave mixed fractions. Elution with Skellysolve B: ether (4 litres, % ether slowly increased from 1% to 40%) gave the methoxyketal 163 (12.65 gms, 71%). Further elution with 40% ether in Skellysolve B gave first (750 ml) mixed fractions and then (1500 ml) gave the ketal 131 (500 mg).

#### The Methoxy Ketone 164.

The methoxy ketal 163 (31 gms, 96 mmoles) was stirred in methanol (300 ml), conc. hydrochloric acid (175 ml), and water (400 ml) for 24 hours. The solution was basified with potassium carbonate and extracted with ether (100 ml, five times). The ethereal solution was dried ( $\text{MgSO}_4$ ) and concentrated to a yellow viscous oil (24.1 gms, 90%) which







crystallised on standing: mp 48-53°; ir (CCl<sub>4</sub>) 1110 cm<sup>-1</sup> (OCH<sub>3</sub>), 1720 cm<sup>-1</sup> (C=O), 2700, 2775, 2820, 2825 cm<sup>-1</sup> (Bohlmann bands); nmr (CDCl<sub>3</sub>) τ 9.00 (3H, d, J=6 cps, CH-CH<sub>3</sub>), 6.82 (2H, d, J=6 cps, CH<sub>2</sub>-OMe), 6.68 (3H, s, OCH<sub>3</sub>); mass spectrum (180° heated inlet) m/e (rel. intensity) 279(1), 192(100), 164(13); Anal. calcd for C<sub>17</sub>H<sub>29</sub>NO<sub>2</sub>: C, 73.08; H, 10.46; N, 5.01. Found: C, 72.75; H, 10.32; N, 4.72; mp (hydropерchlorate from ethyl acetate) 128-131°.

#### The Cleavage of the Methyl Ether 164.

##### A. Boron trifluoride etherate.

The methoxy ketone 164 (170 mg) was dissolved in ether (5 ml) to which was added acetic anhydride (6 ml) and boron trifluoride etherate (3 ml). The reaction mixture was stirred for four days. Ether (50 ml) was added and the solution shaken with ammonium hydroxide (25 ml, 10%) for five minutes. The ethereal solution was dried (MgSO<sub>4</sub>) and concentrated to an oil (200 mg). Tlc indicated two components, one of which had the same R<sub>F</sub> value as the starting material. Ir (CCl<sub>4</sub>) 1110 cm<sup>-1</sup> (OCH<sub>3</sub>), 1225, 1760 cm<sup>-1</sup> (acetate), 1600 cm<sup>-1</sup> (C=C), 1720 cm<sup>-1</sup> (C=O) and nmr (CDCl<sub>3</sub>) τ 9.0 (d, J=6 cps, CH-CH<sub>3</sub>) 8.0 (s, OAc), 6.82 (d, J=6 cps, CH<sub>2</sub>-OMe) 6.68 (s, OCH<sub>3</sub>), 4.93 (s, C=CH) indicated a mixture of unreacted starting material and its enol acetate.



The product was stirred for one hour in 2% methanolic potassium hydroxide solution, the methanol evaporated, water (50 ml) added, and extracted with ether (50 ml, three times). The ether was dried ( $\text{MgSO}_4$ ) and evaporated to a viscous oil (133 mg) which was homogeneous (by tlc) and identical with the starting material (by ir and tlc).

#### B. Boron tribromide.

The methoxy ketone 164 (70 mg, 0.25 mmoles) was dissolved in dichloromethane (8 ml) to which boron tribromide (1.5 ml) was added with stirring. A white precipitate formed instantly. After stirring for 17 hours the reaction was diluted with dichloromethane (100 ml) and ether added dropwise with stirring until violent reaction had ceased. Ammonium hydroxide solution (10%, 100 ml) was added. The mixture was separated and the aqueous portion washed with dichloromethane (75 ml, twice). All the dichloromethane extracts were dried ( $\text{MgSO}_4$ ) and concentrated to a gum (63 mg, 95%) which was identical with the hydroxy ketone (by ir, tlc, and mp of the hydroperchlorate).

#### The Methoxy Bromoketone 165.

The methoxy ketone 164 (3.372 gms, 12 mmoles) was dissolved in methanol (100 ml) and acidified with conc. hydrobromic acid (48%). The methanol was evaporated to



give a non-crystalline froth: ir ( $\text{CHCl}_3$ )  $1110\text{ cm}^{-1}$  ( $\text{OCH}_3$ ),  $1723\text{ cm}^{-1}$  ( $\text{C=O}$ ),  $2600\text{ cm}^{-1}$  ( $\text{N}^{\oplus}\text{H}$ ). The salt was dissolved in chloroform (50 ml) to which bromine (2.515 gms, 12.7 mmoles) was added at such a rate that the red bromine colour did not persist (approx. one hour). The solution was evaporated, leaving a light brown froth (5.508 gms): ir ( $\text{CHCl}_3$ )  $1110\text{ cm}^{-1}$  ( $\text{OCH}_3$ ),  $1741\text{ cm}^{-1}$  ( $\text{C=O}$ ),  $2600\text{ cm}^{-1}$  ( $\text{N}^{\oplus}\text{H}$ ). 1.3 equivalents of bromine were found to give the purest product. Less than 1.3 equivalents led to unbrominated material (by tlc comparison of the free base with starting material), and more than 1.3 equivalents led to dibrominated material (peak at  $1752\text{ cm}^{-1}$  in the ir).

The Methoxy  $\alpha,\beta$ -Unsaturated Ketone 166.

The methoxy bromoketone hydrobromide 165 (5.5 gms, 12 mmoles) and semicarbazide (2.0 gms, 25 mmoles) were dissolved in glacial acetic acid (125 ml) and heated to reflux temperature under carbon dioxide over fifteen minutes. Fifty percent pyruvic acid (30 ml) was added and the refluxing continued for another twenty minutes under carbon dioxide. The reaction mixture was cooled, diluted with water (500 ml) and basified with conc. ammonium hydroxide. The solution was extracted with ether (75 ml, five times), dried ( $\text{MgSO}_4$ ), and evaporated to give a black tar (2.64 gms). The tar was purified by column chromato-



graphy on alumina. Elution with benzene (50 ml) gave unidentifiable non-polar material. Further elution with benzene (500 ml, 10 fractions) gave a mixture of three components with very similar  $R_F$  values. The components were assumed to be the enol acetate and the methoxy ketone 164 (later separated), and the methoxy  $\alpha,\beta$ -unsaturated ketone 166 (total 1.5 gms, 45% from the methoxyketone 164):  
uv max (95% ethanol) 244 m $\mu$  (theoretical 255 m $\mu$ ); ir (CCl<sub>4</sub>) 1110 cm<sup>-1</sup> (OCH<sub>3</sub>), 1625, 1680 cm<sup>-1</sup> (C=C-C=O); nmr (CCl<sub>4</sub>)  $\tau$  8.92 (t(2d), CH-CH<sub>3</sub>) 6.84 (d, J=6 cps, CH<sub>2</sub>OMe), 6.70 (d(2s), OCH<sub>3</sub>), 4.30 (broad s, C=CH).

Elution with 10% ether:benzene (100 ml) gave mixed fractions and still further elution (250 ml) gave a polar compound showing hydroxyl absorption in the ir, but which was not identified.

#### The Methoxy Ketones 167 and 168.

The methoxy  $\alpha,\beta$ -unsaturated ketone mixture (1.5 gms) in ether (20 ml) was added dropwise to liquid ammonia (250 ml, redistilled) and lithium (1.0 gm) with stirring. The solution was stirred for one hour and ammonium chloride added until the blue colour disappeared. The dry ice-acetone condenser was removed and the ammonia allowed to evaporate. The residue was taken up in water (100 ml) and extracted with ether (75 ml, four times), dried (MgSO<sub>4</sub>), and evaporated to a viscous oil (1.43 gms) which was shown







to be composed of two components (by tlc). The components were separated by column chromatography on alumina. Elution with benzene (25 ml) gave non-polar material. Further elution with benzene (25 ml) gave the methoxy ketones 167 and 168 with the cis-trans hexahydrojulolidine structure (600 mg, two diastereoisomers with almost identical  $R_F$  values by tlc). Further elution with benzene (25 ml) gave a mixed fraction. Elution with 4% ether-benzene (75 ml) gave unreduced methoxy  $\alpha,\beta$ -unsaturated ketone (the  $\alpha,\beta$ -unsaturated ketone absorption still showed in the ir) and the methoxyketone with the cis-cis-hexahydrojulolidine structure.

The last three fractions were reduced by the same procedure and the product (508 mg) chromatographed on alumina. Unreduced material was again obtained, reduced again and chromatographed. All the desired product was combined (606 mg, 18% yield of the methoxyketones with the cis-trans structure from the methoxyketones with the cis-cis structure).

The hydroperchlorate was prepared (perhaps of only one diastereoisomer): mp 193-194°; Anal. calcd for  $C_{17}H_{29}NO_2 \cdot HClO_4$ ; C, 53.74; H, 7.96; N, 3.69. Found: C, 53.31; H, 7.80, N, 3.22. The free base: ir ( $CCl_4$ ) 1110  $cm^{-1}$  ( $OCH_3$ ), 1720  $cm^{-1}$  (C=O), 2820  $cm^{-1}$  ( $OCH_3$ ); nmr ( $CDCl_3$ )  $\tau$  8.90 (3H, q, (2d),  $J=6.5$  cps,  $CH-CH_3$ ), 6.68 (3H, d(2s),  $OCH_3$ ); mass



spectrum (185° heated inlet) m/e (rel. intensity) 279(1), 192(100), 164(3).

The Alcohols 169 and 170.

The methoxy ketones 167 and 168 (506 mg, 1.82 mmoles) were dissolved in dichloromethane (25 ml) and cooled to 0° in ice. Boron tribromide (approx. two equivalents, 900 mg, weight not accurate due to reactivity of the reagent) in dichloromethane (25 ml) was added dropwise over one hour. A white precipitate appeared as the boron tribromide was added. The reaction mixture was stirred for four hours. Ether was added dropwise until the violent reaction ceased. More dichloromethane (50 ml) and conc. ammonium hydroxide (100 ml) were added and separated. The aqueous layer was extracted with dichloromethane (50 ml, four times). All the organic extracts were combined, dried ( $\text{MgSO}_4$ ), and evaporated to give white crystals (487 mg). Tlc indicated two components which were separated by column chromatography on alumina. Elution with dichloromethane (25 ml) gave non-polar material. Further elution (15 ml) gave crystalline alcohol 169 (95 mg, 20%). The next two fractions eluted with dichloromethane (2 x 15 ml) gave a mixture of both alcohols. Elution with 10% chloroform:dichloromethane (75 ml) gave the alcohol 170 (115 mg, 23%). Further elution gave unrecognisable polar material.



The yields varied considerably, alcohol 169 varying between 5 and 20%, and alcohol 170 between 15 and 32%. The combined yield was found to be much lower when longer reaction times, higher temperatures, and a larger excess of boron tribromide were used.

Alcohol 169: ir ( $\text{CCl}_4$ )  $1700\text{ cm}^{-1}$  (C=O),  $3100\text{ cm}^{-1}$  (OH); nmr ( $\text{CDCl}_3$ )  $\tau$  9.05 (d,  $J=5.5$  cps,  $\text{CH}-\text{CH}_3$ ); mass spectrum ( $185^\circ$ , direct probe) m/e (rel. intensity) 265(1), 192(100);

Alcohol 170: ir ( $\text{CHCl}_3$ )  $1720\text{ cm}^{-1}$  (C=O)  $3100\text{ cm}^{-1}$  (OH); nmr ( $\text{CDCl}_3$ )  $\tau$  8.96 (d,  $J=5.5$  cps,  $\text{CH}-\text{CH}_3$ ); mass spectrum ( $185^\circ$ , heated inlet) m/e (rel. intensity) 265(1), 192(100).

#### The Acetate 171.

The alcohol 169 (570 mg, 2.1 mmoles) was stirred in pyridine (7 ml) and acetic anhydride (5 ml) for three hours. At the end of this time the liquid was evaporated to give a brown gum (670 mg). Tlc indicated a pure compound; hydroperchlorate; mp (from acetone)  $192-194^\circ$ ; Anal. calcd for  $\text{C}_{18}\text{H}_{29}\text{NO}_3$ : C, 53.01; H, 7.41; N, 3.43. Found: C, 52.88; H, 7.08; N, 2.92.

#### The Acetate 172.

The alcohol 170 (425 mg, 1.6 mmoles) was acetylated in the same manner as above to yield a pure compound (497 mg): ir ( $\text{CCl}_4$ ) 1235,  $1745\text{ cm}^{-1}$  (acetate),  $1720\text{ cm}^{-1}$  (C=O); mass spectrum ( $200^\circ$ , heated inlet); m/e (rel.



intensity) 307(1), 192(100).

#### Tosylation of Alcohol 170

The alcohol 170 (125 mg, 0.47 mmoles) was dissolved in dichloromethane (5 ml) to which p-toluenesulphonyl chloride (134 mg, 0.70 mmoles) and pyridine (1 ml) were added. The solution was stirred for 24 hours and then taken up in dichloromethane (50 ml) and washed with potassium carbonate solution (50 ml, 10%). The organic layer on evaporation gave no residue. The aqueous layer was continuously extracted with dichloromethane for four days. On evaporation, the dichloromethane extract gave a crystalline residue (105 mg): mp (from acetone) 278-279°; ir (nujol) 675, 1005, 1024, 1114, 1185, 1198  $\text{cm}^{-1}$  (toluene sulphonate ion), 1718  $\text{cm}^{-1}$  (C=O); nmr ( $\text{D}_2\text{O}$ )  $\tau$  8.80 (3H, d,  $J=6$  cps) 7.70 (3H, s, aromatic methyl, 2.9, 2.5 (4H, q, aromatic  $\text{A}_2\text{B}_2$  system); Anal. calcd for  $\text{C}_{23}\text{H}_{33}\text{NO}_4\text{S}$ : C, 65.77; H, 7.92; N, 3.34: Found C, 66.07; H, 7.86; N, 3.55.

The alcohol 169 when reacted in the same way gave a water soluble product which was similar in ir and nmr but which was not further purified.

#### Attempted Formation of the Benzyl Salt of the Hydroxyketone 144.

The hydroxyketone 144 (150 mg, 0.57 mmoles) and benzyl bromide (145 mg, 0.85 mmoles) were refluxed in acetone (10







ml) for 48 hours under anhydrous conditions. The solution was evaporated to dryness to yield starting material (by tlc and ir).

The reaction was repeated, using dry acetonitrile as solvent, with identical results. When methanol was used as solvent the hydrobromide was obtained (by ir and basification to starting material).

#### Attempted Ring Closure Using the Hydrobromide.

##### A. Conc. hydrobromic acid treatment of the hydroxyketone

The hydroxyketone 144 (200 mg) was refluxed in conc. hydrobromic acid (5 ml, 48%) for five hours. The acid was then evaporated to yield a semi-crystalline residue. Recrystallisation from acetone gave impure crystals. Further recrystallisation using ethyl acetate gave pure crystals: mp 282-284°; ir ( $\text{CHCl}_3$ )  $1725\text{ cm}^{-1}$  (C=O),  $2500\text{--}2700\text{ cm}^{-1}$  ( $\text{N}^{\oplus}\text{H}$ ); nmr ( $\text{CDCl}_3$ )  $\tau$  8.79 (d,  $J=5.5$  cps,  $\text{CH}-\underline{\text{CH}_3}$ ); Anal. Calcd for  $\text{C}_{16}\text{H}_{27}\text{Br}_2\text{NO}$ : Br, 39.05; Found: Br, 38.60.

##### B. Conc. hydrobromic acid treatment of the alcohols 169 and 170.

The alcohols 169 and 170 (25 mg) were separately reacted as above to give approximately 33 mg of gum in each case. The ir's were similar showing absorptions at  $1725\text{ cm}^{-1}$  (C=O) and  $2500\text{--}2700\text{ cm}^{-1}$  ( $\text{N}^{\oplus}\text{H}$ ).



C. Treatment of the Bromides with Potassium Tertiary Butoxide.

The bromo compounds formed above were separately reacted with potassium tertiary butoxide (30 mg, 3 molar equivs) in tertiary butyl alcohol (5 ml). The reaction mixtures were refluxed for fifty minutes, diluted with water (50 ml) and extracted with ether (50 ml, five times). The ether extract was dried ( $\text{MgSO}_4$ ) and evaporated to a brown gum in both cases (9-11 mg). The tlc of both indicated the possible presence of the ring closed product 133. The mass spectrum of each had peaks at m/e 247 and m/e 190 indicating ring closed material. No identifiable products could be separated, however.

Attempted Ring Closure Using N-Methyl for the Blocking Group.

A. Methiodide formation.

The alcohol 170 (100 mg) was refluxed in acetone (10 ml) with a large excess of methyl iodide (2 ml) for three days. On evaporation of the solvent a non-crystalline mixture was obtained. Tlc showed about 20% starting material and about 80% polar material. Treatment with methyl iodide in methanol or in acetonitrile as solvent under the same conditions gave similar yields. When the alcohol 170 was heated with methyl iodide in a sealed tube at  $110^\circ$  for 25 hours similar results were obtained.

B. Treatment of the Methiodide with conc. Hydrobromic Acid.

The crude methiodide from above was refluxed in conc.



hydrobromic acid for five hours. Iodine formed on the inside of the condenser. The solvent was evaporated leaving a brown froth (170 mg).

C. Treatment of the Methobromide with Potassium Tertiary.

Butoxide. The crude methobromide and potassium tertiary butoxide (108 mg, 2.5 molar equiv.) were refluxed in tertiary butyl alcohol under anhydrous conditions for three hours. The tertiary butyl alcohol was evaporated and the residue taken up in methanol (5 ml). The methanol solution was decanted leaving behind insoluble potassium bromide, and then evaporated and the residue sublimed at 200° (0.5 mm). A gummy material (35 mg) was obtained. Tlc and glc (5 x 1/8", QF 1 column at 180°) indicated about five components of which a minor one corresponded to the desired ring closed material.

D. Treatment of the Alcohol 170 with Methyl p-Toluene-sulphonate.

The alcohol 170 (40 mg, 0.15 mmoles) and methyl p-toluenesulphonate (75 mg, 0.40 mmoles) were refluxed in dichloromethane (5 ml) for two days under anhydrous conditions. Tlc indicated no reaction.

The Methoxy Lactams 178 and 179.

The methoxy ketones 167 and 168 (2.79 gms, 10.0 mmoles) were dissolved in acetone (distilled from potassium per-



manganate) at 0°. Potassium permanganate (2.37 gms, 15.0 mmoles) was added portionwise (2 hrs) to the stirred solution at 0°. After the addition was complete the solution was stirred one hour longer and then the acetone evaporated. The residue was dissolved in hydrochloric acid (100 ml, 20%) and extracted with dichloromethane (75 ml, five times). The extract was washed once with sat. sodium bicarbonate solution, dried ( $\text{MgSO}_4$ ), and evaporated to a crude gum (1.06 gms). The acidic aqueous portion was basified with conc. ammonium hydroxide and extracted with ether (50 ml, five times). The ethereal extract was dried ( $\text{MgSO}_4$ ) and evaporated to give almost pure starting material (by tlc and ir, 1.18 gms). This material was re-oxidised under the same conditions to give crude lactam (427 mg) and starting material (465 mg).

In each oxidation the yield of crude lactam was ca. 36% and ca. 40% starting material was recovered. The crude lactam was used in the next reaction but it may be purified by column chromatography on alumina (neutral, activity V). The first few fractions (dichloromethane) eluted contained pure lactam. The lactam could not be crystallised: ir ( $\text{CCl}_4$ ); 1110, 2830  $\text{cm}^{-1}$  ( $\text{OCH}_3$ ), 1650  $\text{cm}^{-1}$  (lactam C=O), 1730  $\text{cm}^{-1}$  (C=O); nmr ( $\text{CDCl}_3$ )  $\tau$  8.95 (3H, t(2d),  $J=6$  cps,  $\text{CH}-\underline{\text{CH}}_3$ ), 6.60-6.80 (5H, 2 sharp s, and m,  $\text{OCH}_3$ ,  $\text{CH}_2\text{OMe}$ ), 5.3 (d,  $J=14$  cps,  $\underline{\text{CH}}-\text{N}-\text{CO}$ , in deshielding cone); mass spectrum (185°







heated inlet) m/e (rel. intensity) 206(100).

The Lactam Alcohols 180 and 181.

The crude methoxy lactam (1.486 gms) was dissolved in dichloromethane (50 ml). Boron tribromide (10 gms) in dichloromethane (40 ml) was added to the stirred solution. A precipitate formed immediately and heat was evolved. The solution was stirred for twelve hours and then ether added dropwise until violent reaction stopped. Dil. ammonium hydroxide (100 ml, 10%) was added and the solution extracted with dichloromethane (100 ml, four times). The organic extract was washed once with dil. hydrochloric acid (1N, 50 ml) and once with sodium bicarbonate solution (50 ml). The extract was dried ( $\text{MgSO}_4$ ) and evaporated to a gum (1.0 gm). The gum was purified by column chromatography on alumina (neutral, activity V). Elution with dichloromethane (four fractions, 10 ml each) gave non polar material. Further elution with dichloromethane (seven fractions, 25 ml each) gave pure non-crystalline product (529 mg, 13.5% from the methoxy ketones 167 and 168 or 71% from pure methoxy lactam); ir ( $\text{CHCl}_3$ )  $1630\text{ cm}^{-1}$  (lactam C=O),  $1725\text{ cm}^{-1}$  (C=O), 3400,  $3620\text{ cm}^{-1}$  (OH); nmr ( $\text{CHCl}_3$ )  $\tau$  8.98 (3H, t, (2d),  $J=6.5$  cps,  $\text{CH}-\text{CH}_3$ ), 6.5 (2H, m,  $\text{CH}_2\text{OH}$ ), 5.3 (1H, q, (2d),  $J=15$  cps,  $\text{CH}-\text{N}-\text{CO}$ ); mass spectrum ( $160^\circ$ , direct probe) m/e (rel. intensity) 279(1), 261(5), 206(100).



Attempted Tosylation of the Lactam Alcohols 180 and 181.

The lactam alcohols 180 and 181 (100 mg, 0.36 mmoles) and p-toluenesulphonyl chloride (104 mg, 0.55 mmoles) were stirred in dry pyridine (7 ml) for three days. Shorter reaction times gave starting material. The reaction mixture was poured into dichloromethane (50 ml) and extracted once with hydrochloric acid (25 ml, 1N) and once with sat. sodium bicarbonate solution. The organic layer was dried ( $\text{MgSO}_4$ ) and evaporated to a non-crystalline gum (73 mg). Tlc indicated two main components with very similar  $R_F$  values. The two components were separated by column chromatography on alumina (neutral, activity V). Elution with benzene (100 ml) gave the first component (5.0 mg) pure: ir ( $\text{CHCl}_3$ )  $1630\text{ cm}^{-1}$  (lactam C=O),  $1720\text{ cm}^{-1}$  (C=O), mass spectrum ( $150^\circ$ , direct probe) m/e (rel. intensity) 361(1), 207(18), 206(100). Elution with dichloromethane (50 ml) gave the lactam tosylates 182 and 183 (5.0 mg): ir ( $\text{CHCl}_3$ )  $1170$ ,  $1450\text{ cm}^{-1}$  (sulphonate),  $1625\text{ cm}^{-1}$  (lactam C=O),  $1720\text{ cm}^{-1}$  (C=O); nmr ( $\text{CDCl}_3$ , of both components)  $\tau$  8.85-9.05 (q,  $\text{CH}-\underline{\text{CH}}_3$ ), 7.52 (s, aromatic methyl), 6.10 (broad,  $\text{CH}_2\text{OSO}_2-$ ) 5.4 (broad,  $\underline{\text{CH}}-\text{N}-\text{CO}$ ), 2.2, 2.6 (2d, aromatic H).

The Mesyl Lactams 185 and 186.

The lactam alcohols 180 and 181 (366.8 mg, 1.32 mmoles) were dissolved in dry pyridine (10 ml). Mesyl chloride (75 drops) was added at  $0^\circ$  and left at  $0^\circ$  for 10 minutes. The



reaction mixture was diluted with dichloromethane (100 ml) and washed with hydrochloric acid (1N, 50 ml, twice). The organic layer was dried ( $\text{MgSO}_4$ ) and evaporated to a non-crystalline gum (544 mg). It was purified by column chromatography on alumina (neutral, activity V). Elution with benzene (50 ml) gave non-polar material. Elution with benzene:dichloromethane (1:1, 150 ml) gave the pure mesylate 185 and 186 (298 mg, 63%): ir ( $\text{CHCl}_3$ ) 1175, 1350, 1365  $\text{cm}^{-1}$  (sulphonate), 1640  $\text{cm}^{-1}$  (lactam C=O), 1740  $\text{cm}^{-1}$  (C=O): nmr ( $\text{CDCl}_3$ )  $\tau$  7.9 (m,  $\text{CH}-\underline{\text{CH}}_3$ ) 6.92 (d(2s),  $\text{SO}_2\text{CH}_3$ ), 5.9 (broad,  $\text{CH}_2-\text{OSO}_2$ ); 5.25 (broad d,  $\underline{\text{CH}}-\text{N}-\text{CO}$ ).

Longer reaction times or higher temperatures led to added impurities and lower yields. Tlc of the pure material showed two components with almost identical  $R_F$  values.

#### The Lactams 177 and 184.

The mesyl lactam (298 mg, 0.83 mmoles) and potassium tertiary butoxide (230 mg, 2.1 mmoles prepared by dissolving potassium in dry tertiary butyl alcohol were refluxed under nitrogen for 15 minutes. The reaction mixture was acidified with 1N hydrochloric acid and evaporated. The residue was taken up in water (100 ml) and extracted with dichloromethane (50 ml, three times), dried ( $\text{MgSO}_4$ ) and evaporated to a gum (222 mg). The tlc indicated four components, the major one being of the same  $R_F$  value as the authentic lactam 177. The components were separated by column chromatography.





Elution with benzene (30 ml) gave pure component 1 (10.0 mg): ir ( $\text{CHCl}_3$ )  $1150, 1370 \text{ cm}^{-1}, 1625 \text{ cm}^{-1}$  (lactam  $\text{C=O}$ ),  $1725 \text{ cm}^{-1}$  ( $\text{C=O}$ ); mass spectrum ( $170^\circ$ , direct probe) m/e (rel. intensity) 278(29; mass = 278.1757, calcd = 278.1756  $\text{C}_{16}\text{H}_{24}\text{NO}_3$ ), 276(33; mass = 276.1604, calcd = 276.1600,  $\text{C}_{16}\text{H}_{22}\text{NO}_3$ ), 232(87), 222(100; mass = 222.1130, calcd = 222.1130  $\text{C}_{12}\text{H}_{16}\text{NO}_3$ ), 220(33), 176(33).

Further elution with benzene (30 ml) gave pure component 2 (7.0 mg); ir ( $\text{CHCl}_3$ )  $1160, 1370 \text{ cm}^{-1}, 1625 \text{ cm}^{-1}$  (lactam  $\text{C=O}$ ),  $1720 \text{ cm}^{-1}$  ( $\text{C=O}$ ); mass spectrum ( $195^\circ$ , direct probe (m/e rel. intensity) 278(28; mass = 278.1754, calcd = 278.1756,  $\text{C}_{16}\text{H}_{24}\text{NO}_3$ ), 276(28; mass = 276.1599, calcd = 276.1600,  $\text{C}_{16}\text{H}_{22}\text{NO}_3$ ), 232(92) 222(100; mass = 222.1132, calcd = 222.1130,  $\text{C}_{12}\text{H}_{16}\text{NO}_3$ ), 220(28), 176(41).

Further elution with benzene (20 ml) gave mixed fractions and then (200 ml) gave the lactams 177 and 184 (22.0 mg): mp (from ethyl acetate)  $151-152^\circ$  (lactam 177  $142-143^\circ$ ); ir ( $\text{CHCl}_3$ )  $1615 \text{ cm}^{-1}$  (lactam  $\text{C=O}$ ),  $1700 \text{ cm}^{-1}$  ( $\text{C=O}$ ); nmr ( $\text{CDCl}_3$ )  $\tau$  8.97 (3H, d,  $J=6.0 \text{ cps}$ ,  $\text{CH}-\underline{\text{CH}}_3$ ) 5.43 (broad d,  $\underline{\text{CH}}-\text{N}-\text{CO}$ ); mass spectrum ( $170^\circ$ , direct probe) m/e (rel. intensity) 261(33; mass = 261.1730, calcd = 261.1729,  $\text{C}_{16}\text{H}_{23}\text{NO}_2$ ), 204(100), 176(45). The lactam 177 was run under identical conditions: mass spectrum ( $170^\circ$ , direct probe) m/e (rel. intensity) 261(31), 204(100), 176(43).





Further elution with benzene (100 ml) gave pure component 3 (5.0 mg): ir ( $\text{CHCl}_3$ ) 960, 1160, 1350  $\text{cm}^{-1}$ , 1620  $\text{cm}^{-1}$  (lactam C=O), 1710  $\text{cm}^{-1}$  (C=O); mass spectrum (180° direct probe) m/e (rel. intensity) 278(21), 222(100), 176(31).

The Lactam Acetate 188.

The acetate 172 (497 mg, 1.6 mmoles) and anhyd. magnesium sulphate (3.0 gms) were added to acetone (50 ml, distilled from potassium permanganate). Potassium permanganate (380 mg, 2.4 mmoles) was added portionwise over 50 minutes to the stirred suspension at 0°. The reaction mixture was stirred for ten minutes more after the addition. The acetone was evaporated and the residue dissolved in hydrochloric acid (1N, 100 ml). The solution was extracted with dichloromethane (50 ml, five times), dried ( $\text{MgSO}_4$ ), and evaporated to a gum (188 mg). The aqueous portion was basified with ammonium hydroxide solution (10%), extracted with ether (50 ml, five times), dried ( $\text{MgSO}_4$ ), and evaporated to give starting material (135 mg). Tlc indicated that the starting material was half alcohol 170 and half acetate 172. The mixture was acetylated as before and re-oxidised as above to yield neutral lactam (56 mg) and starting material (34 mg). Tlc indicated that the neutral portion was half lactam acetate 188 and half lactam alcohol 181. It was reacted further without purification.



A purified sample showed: ir ( $\text{CCl}_4$ )  $1230, 1750 \text{ cm}^{-1}$  (acetate),  $1650 \text{ cm}^{-1}$  (lactam  $\text{C}=\text{O}$ ),  $1725 \text{ cm}^{-1}$  ( $\text{C}=\text{O}$ ); nmr ( $\text{CDCl}_3$ )  $\tau$  8.96 (3H, d,  $J=6$  cps). 6.07 (2H, d,  $J=6$  cps,  $\text{CH}_2\text{OAc}$ ), 5.25 (1H, d,  $J=14$  cps,  $\text{CH}-\text{N}-\text{CO}$ ).

The Lactam Alcohol 181.

The crude lactam acetate (293 mg) was stirred in 2% methanolic potassium hydroxide and water (one ml) for four hours. The solution was neutralised with 1N hydrochloric acid and the methanol evaporated to a smaller volume. Water (100 ml) was added and the solution extracted with chloroform (50 ml, four times), dried ( $\text{MgSO}_4$ ), and evaporated to a gum (184 mg). The gum was purified by column chromatography on alumina (neutral activity V). Elution with dichloromethane (30 ml) gave non-polar material and then (200 ml) the pure lactam alcohol (57 mg, 19% from acetate 172): ir ( $\text{CHCl}_3$ )  $1620 \text{ cm}^{-1}$  (lactam  $\text{C}=\text{O}$ ),  $1720 \text{ cm}^{-1}$  ( $\text{C}=\text{O}$ ),  $3400, 3610 \text{ cm}^{-1}$  (OH); nmr ( $\text{CDCl}_3$ )  $\tau$  9.0 (3H, d,  $J=6$  cps,  $\text{CH}-\underline{\text{CH}}_3$ ) 6.45 (2H, broad,  $\underline{\text{CH}}_2\text{OH}$ ), 5.20 (1H, d,  $J=14$  cps,  $\underline{\text{CH}}-\text{N}-\text{CO}$ ); mass spectrum ( $180^\circ$ , direct probe) m/e (rel. intensity) 206(100).

The Mesyl Lactam 186.

The lactam alcohol 181 (57 mg, 0.2 mmoles) was reacted as before to yield a non-crystalline gum (43 mg, 0.12 mmoles 60%); ir ( $\text{CHCl}_3$ )  $1170, 1350 \text{ cm}^{-1}$  (sulphonate),  $1630 \text{ cm}^{-1}$  (lactam  $\text{C}=\text{O}$ ),  $1720 \text{ cm}^{-1}$  ( $\text{C}=\text{O}$ ); nmr ( $\text{CDCl}_3$ )  $\tau$  8.95 (3H, broad,  $\text{CH}-\underline{\text{CH}}_3$ ), 6.95 (3H, s,  $\text{SO}_2-\text{CH}_3$ ), 5.93 (2H, broad,



$\text{CH}_2\text{-OSO}_2^-$ ), 5.25 (1H, broad d, CH-N-CO). Tlc indicated only one component.

#### The Lactam 184.

The mesyl lactam 186 (43 mg, 0.12 mmoles) was dissolved in dry tertiary butyl alcohol (5 ml, distilled from sodium) and the solution heated to reflux temperature under nitrogen. Potassium tertiary butoxide (27 mg, prepared by dissolving potassium in dry tertiary butyl alcohol) was added to the solution and the refluxing continued for fifteen minutes. The reaction mixture was then neutralised with 1N hydrochloric acid and the tertiary butyl alcohol evaporated. The residue was taken up in water (50 ml) and extracted with dichloromethane (75 ml, four times). The organic extracts were dried ( $\text{MgSO}_4$ ) and evaporated to a semi-crystalline gum (30 mg). Tlc showed three components, one of which had the same  $R_F$  value as the lactam 177. The components were separated by preparative tlc (alumina H, 1/2 mm plate in chloroform). The edges of the 15 x 15 cm plate were sprayed with iodine in methanol and the alumina separated into three fractions. The fractions were eluted from the absorbent with chloroform (100 ml). Fraction one was mainly component 189 and crystallised (6.0 mg): mp (from ethyl acetate) 177-182°; ir ( $\text{CHCl}_3$ )  $1630\text{ cm}^{-1}$  (lactam C=O),  $1710\text{ cm}^{-1}$  (C=O); mass spectrum (170°, direct probe) m/e (rel. intensity) 261(74), 204(99), 176(100). Fraction two



was sublimed to yield crystalline material which tlc showed to be pure lactam 184 (6.2 mg, 20%): mp (from ethyl acetate) 149-152°; ir (CHCl<sub>3</sub>) 1620 cm<sup>-1</sup> (lactam C=O), 1710 cm<sup>-1</sup> (C=O); mass spectrum (170°, direct probe) m/e (rel. intensity) 261(42; mass = 261.1730, calcd = 261.1729, C<sub>16</sub>H<sub>23</sub>NO<sub>2</sub>), 204(100), 176(60). Fraction three contained lactam 184 and a component which was not identified.

#### The Lactam Acetate 187.

The acetate 171 (674 mg, 2.2 mmoles) was oxidised with potassium permanganate under conditions identical with those used for acetate 172 to give crude lactam acetate 187 plus lactam alcohol 180 (185 mg) and acetate 171 plus alcohol 169 (45 mg). The crude product was not purified or characterised.

#### The Lactam Alcohol 180.

The crude lactam from above (185 mg) was hydrolysed under conditions identical with those used for lactam acetate 188 to give crude lactam alcohol (69 mg). The product was purified by column chromatography on alumina (neutral, activity V). Elution with dichloromethane (100 ml) gave fractions of non-polar material. Further elution with dichloromethane (100 ml) gave non-crystalline lactam alcohol 180 (14.0 mg, 0.05 mmoles, 2.5% from the acetate 171); ir (CHCl<sub>3</sub>) 1620 cm<sup>-1</sup> (lactam C=O), 1715 cm<sup>-1</sup> (C=O).







The Mesyl Lactam 185.

The lactam alcohol 180 (14.0 mg, 0.05 mmoles) was treated with mesyl chloride under conditions identical with those used for the lactam alcohol 181 to give the pure mesyl lactam 185 (14.0 mg, 0.04 mmoles, 80%). Tlc indicated only one pure component with  $R_F$  value identical with mesyl lactam 186 and the mixture of mesyl lactams 185 and 186.

The Lactam 177.

The mesyl lactam 185 (14.0 mg, 0.04 mmoles) was treated under conditions identical with those used for the mesyl lactam 186 to give a gum (9.0 mg). Tlc showed one major component and two minor ones with lower  $R_F$  values. The components were separated by preparative tlc (alumina H, 1/2 mm) in chloroform. The alumina was separated into two fractions and eluted from the absorbent with chloroform (100 ml). Fraction two (1.0 mg) was a pure minor component; mass spectrum (170°, direct probe) m/e (rel. intensity) 261(11), 247(60), 204(44), 190(16), 176(49), 162(100), 149(86). Fraction one was a pure crystalline compound (3.7 mg, 0.014 mmoles, 36%). Tlc showed it to be identical in  $R_F$  value with the natural lactam 177 (chloroform and ethyl acetate as solvents, alumina plates); mp (from ethyl acetate) 157-158°; mixed mp with the natural lactam: 150-154°; ir ( $\text{CHCl}_3$ )  $1615\text{ cm}^{-1}$  (lactam C=O),  $1700\text{ cm}^{-1}$  (C=O), identi-



cal with the ir of the natural lactam 177; mass spectrum  
(170°, direct probe) m/e (rel. intensity) 261(32; mass =  
261.1730, calcd = 261.1729, C<sub>16</sub>H<sub>23</sub>NO<sub>2</sub>).



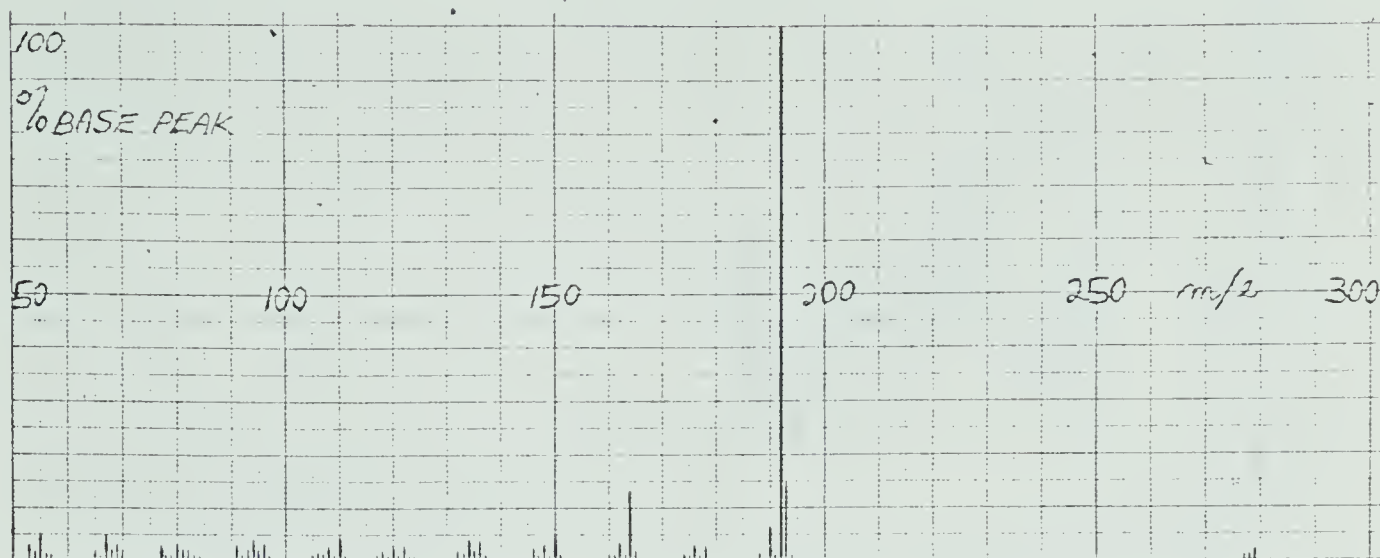


Fig. 15 The Methoxy Ketone 164

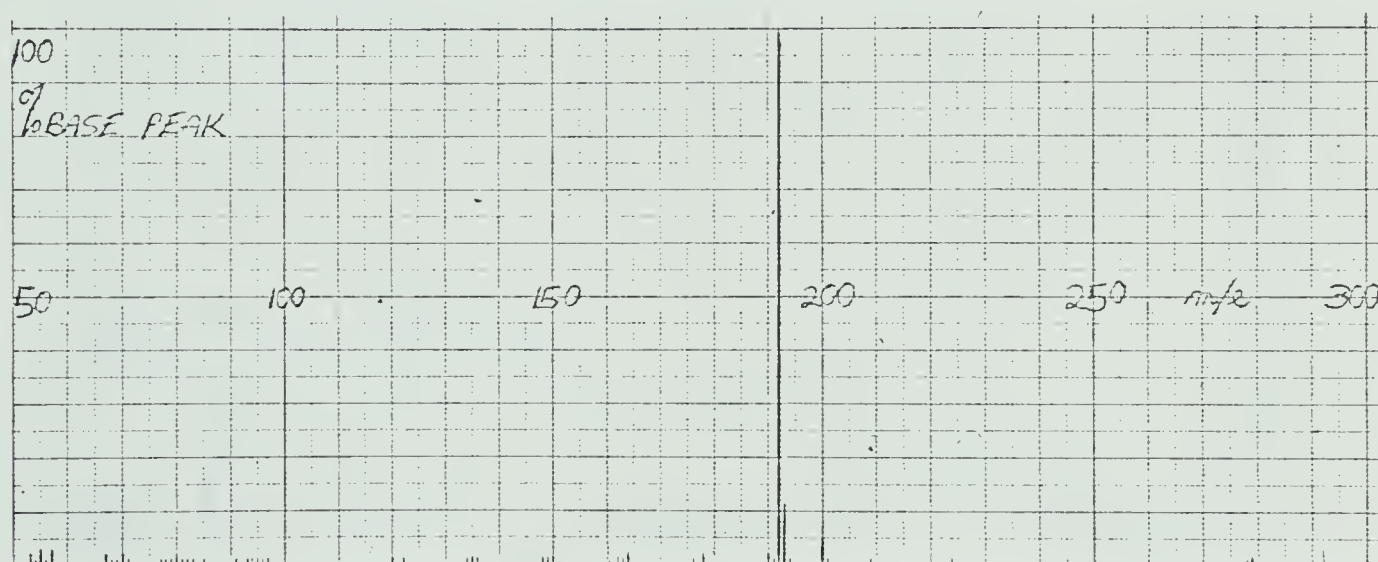


Fig. 16 The Methoxy Ketones 167 and 168

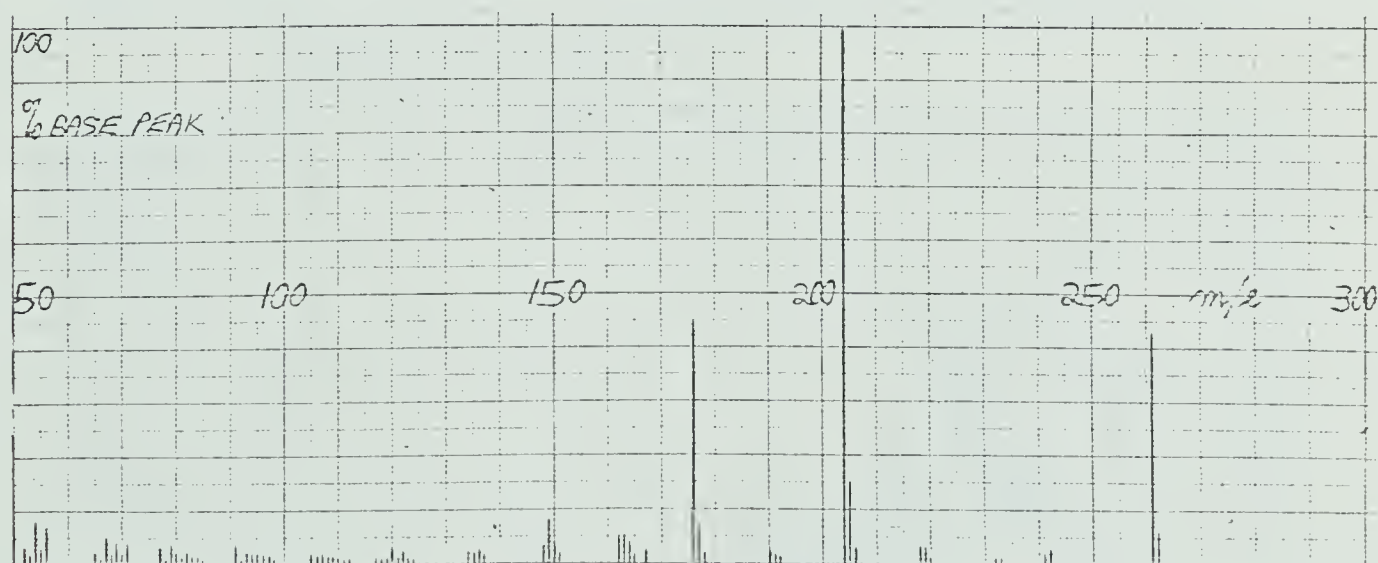


Fig. 17 The Lactams 177 and 184



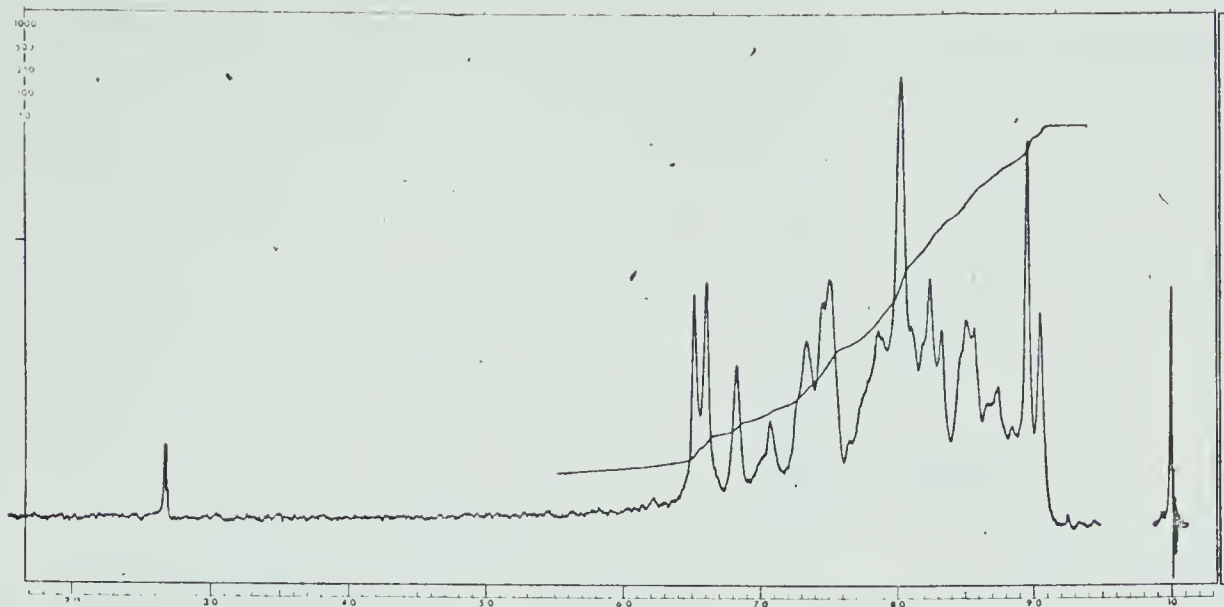


Fig. 18 The Hydroxy Ketone 142

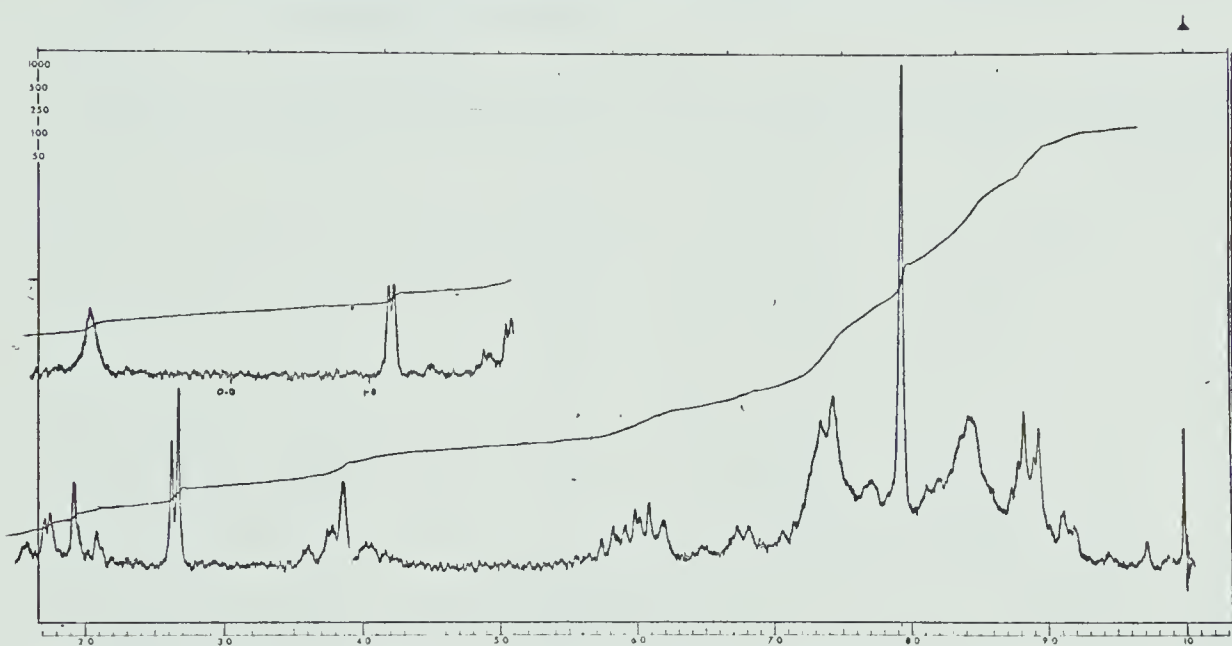


Fig. 19 The Acetoxy  $\alpha,\beta$ -Unsaturated 2,4-Dinitrophenylhydrazone 154.

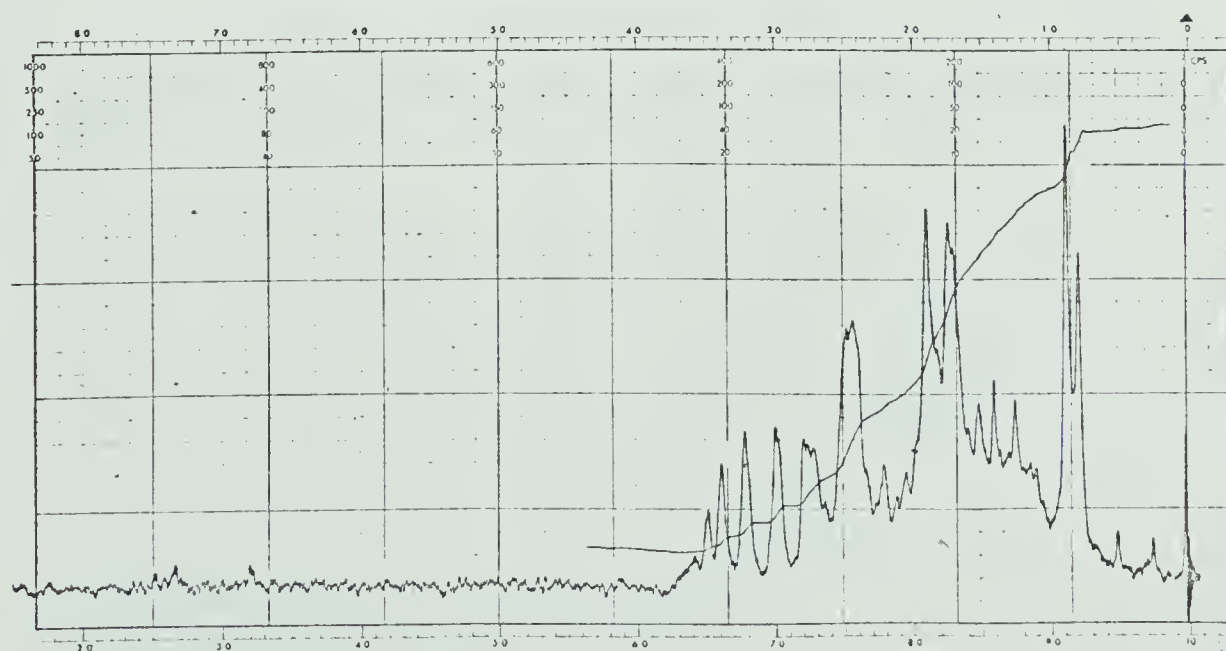


Fig. 20 The Ether 160





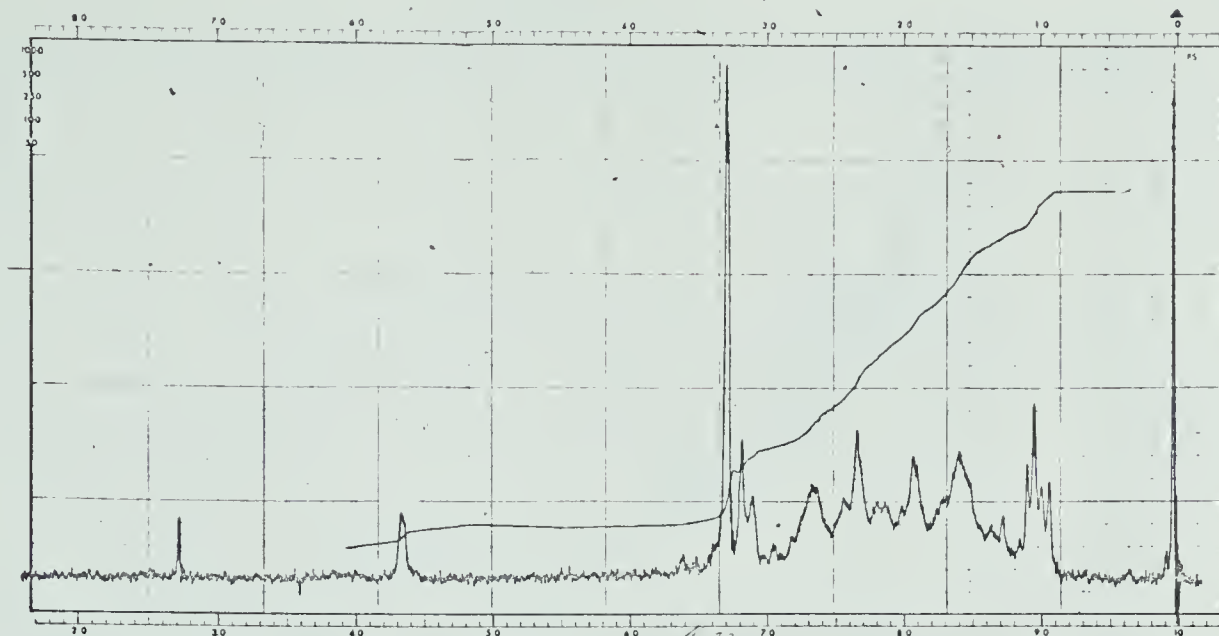


Fig. 21 The Methoxy  $\alpha,\beta$ -Unsaturated Ketone Reaction Mixture 166.

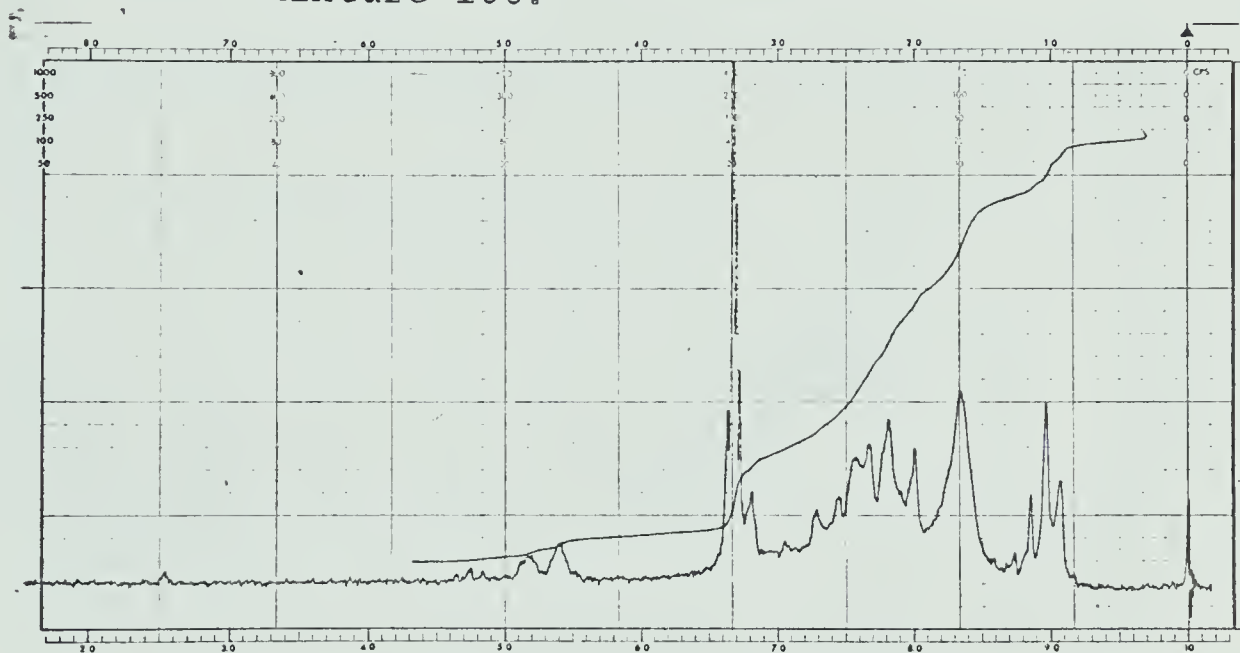


Fig. 22 The Methoxy Lactams 178 and 179

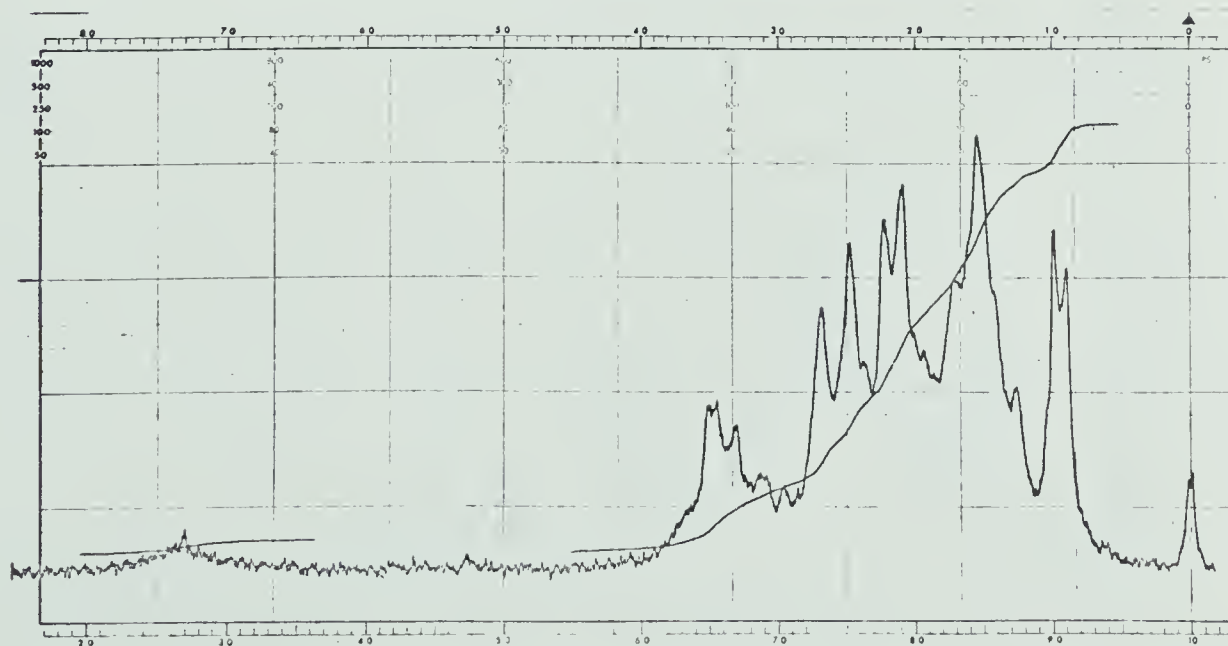


Fig. 23 The Alcohol 169



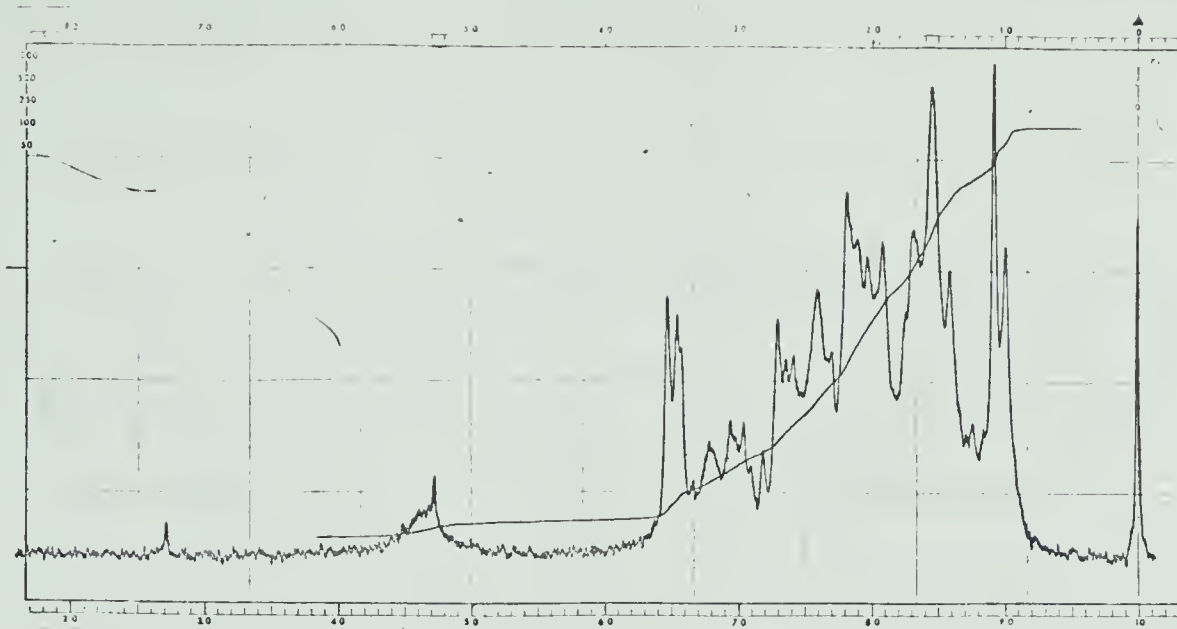


Fig. 24 The Alcohol 170

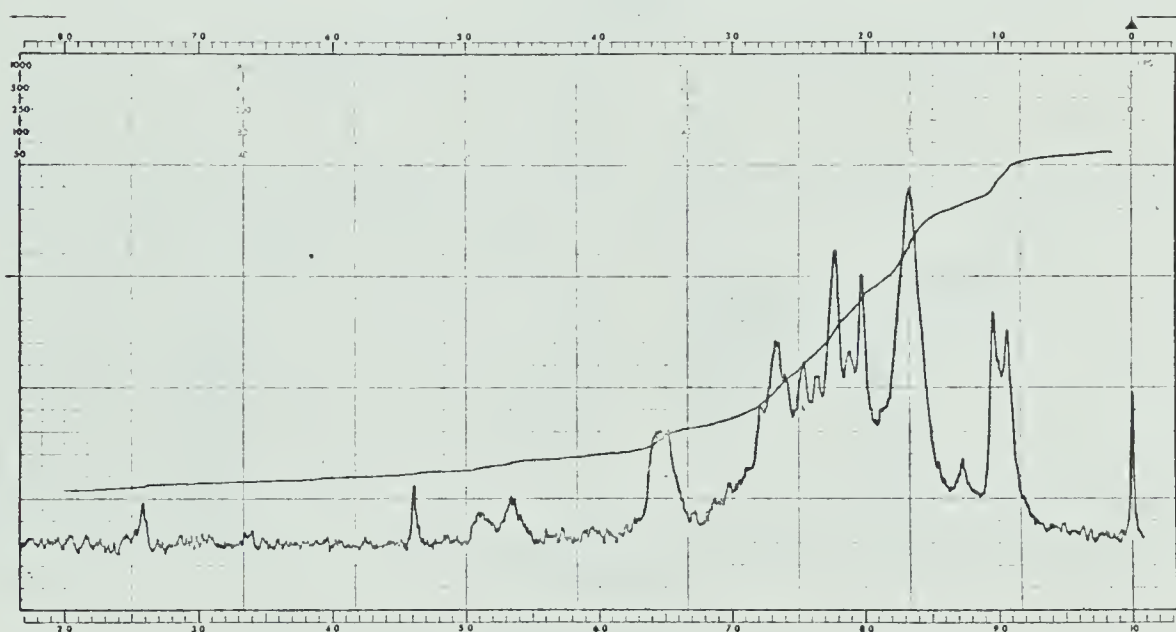


Fig. 25 The Lactam Alcohol 181

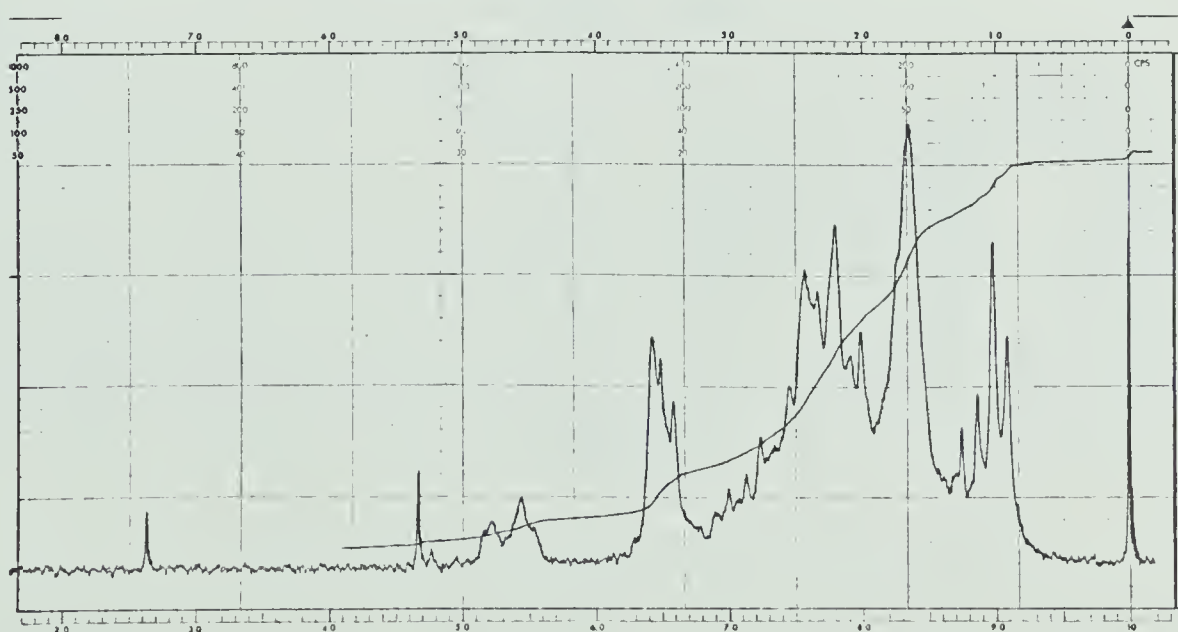


Fig. 26 The Lactam Alcohols 180 and 181



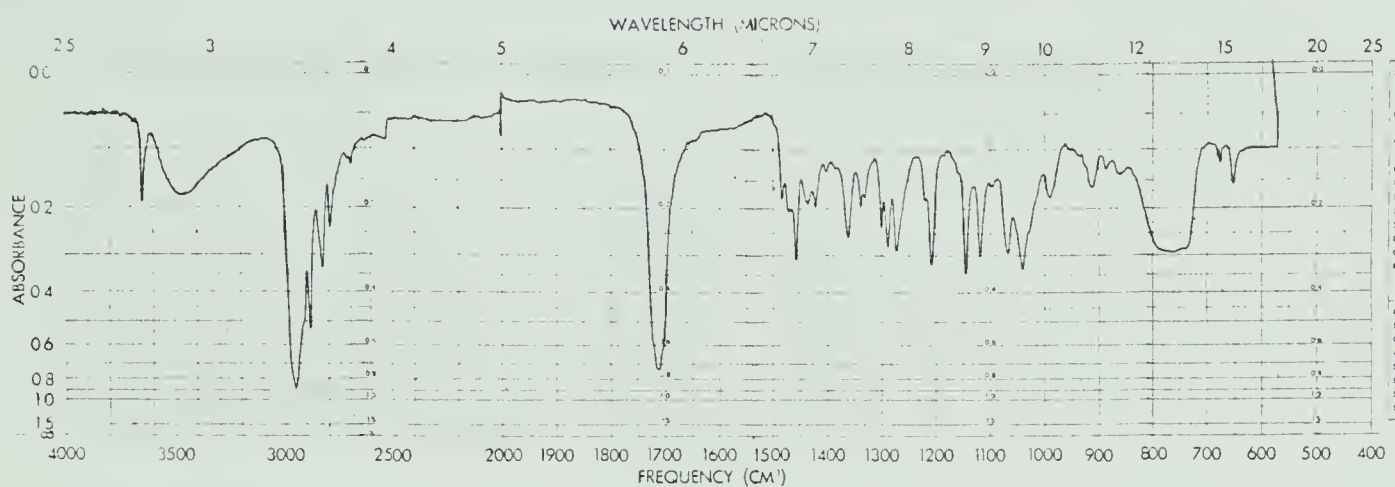


Fig. 27 The Hydroxy Ketone 142

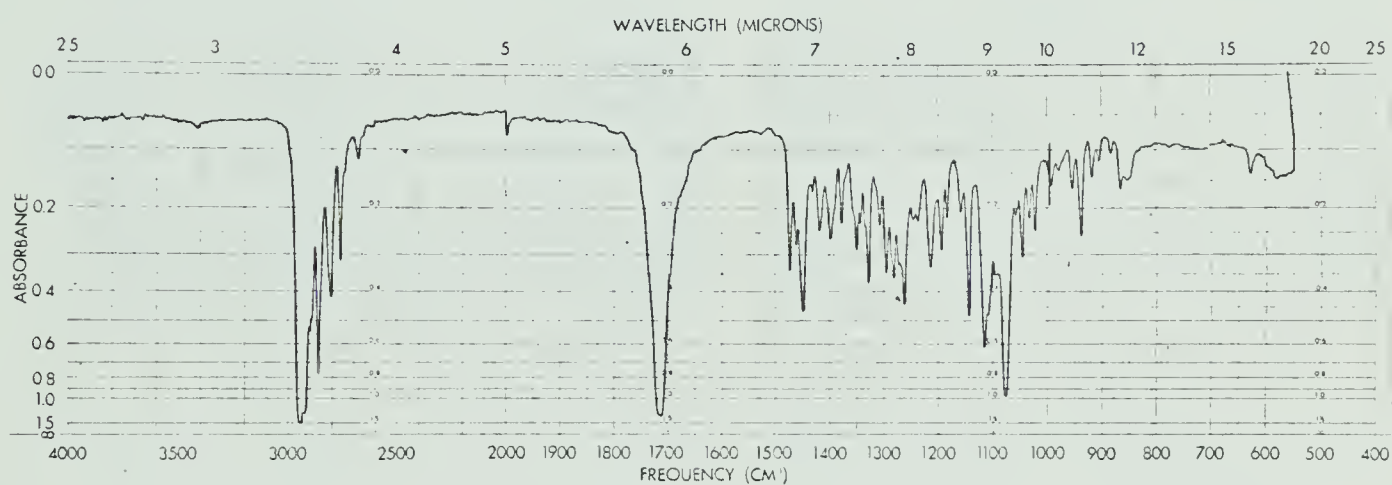


Fig. 28 The Ether 160

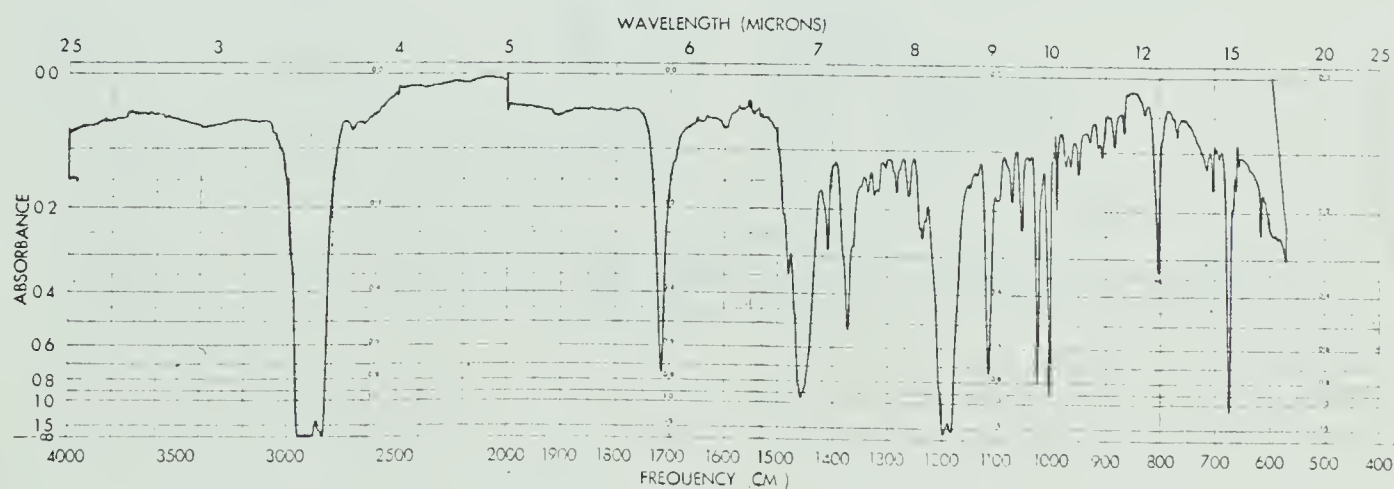


Fig. 29 The Quaternary Salt 174



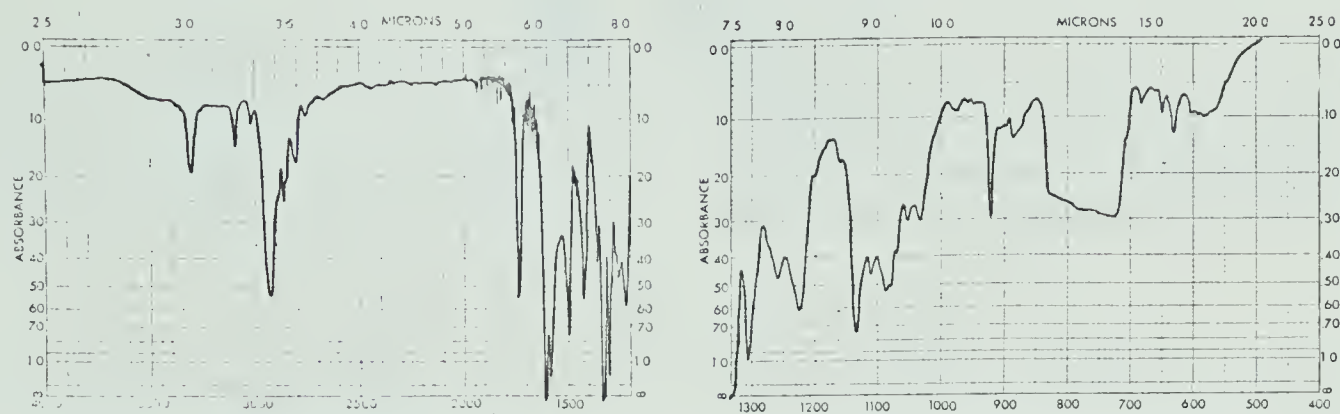


Fig. 30 The Acetoxy  $\alpha,\beta$ -Unsaturated 2,4-Dinitrophenylhydrazone 154

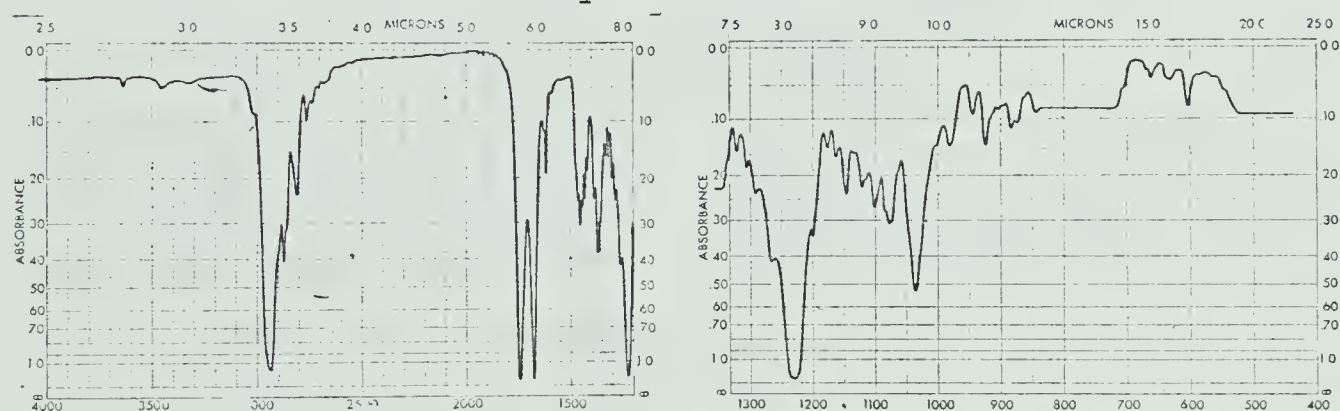


Fig. 31 The Acetoxy  $\alpha,\beta$ -Unsaturated Ketone 159

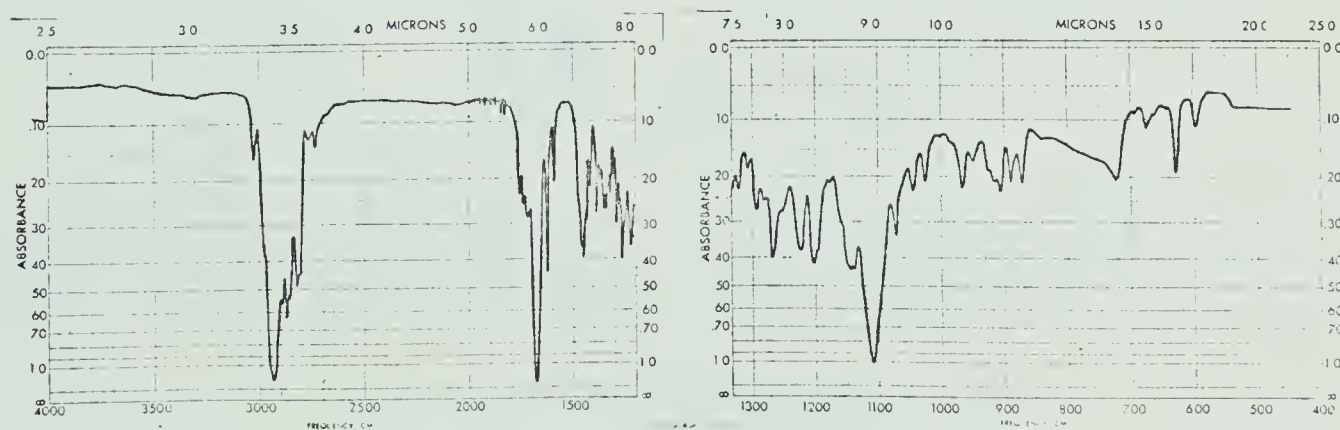


Fig. 32 The Methoxy  $\alpha,\beta$ -Unsaturated Ketone Reaction Mixture 166





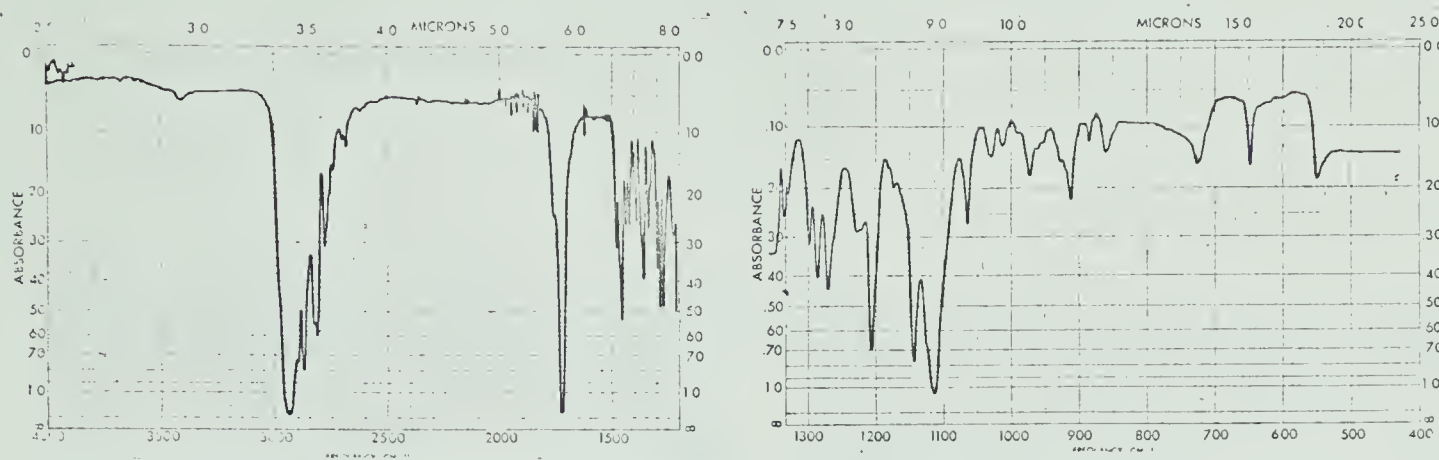


Fig. 33 The Methoxy Ketone 164

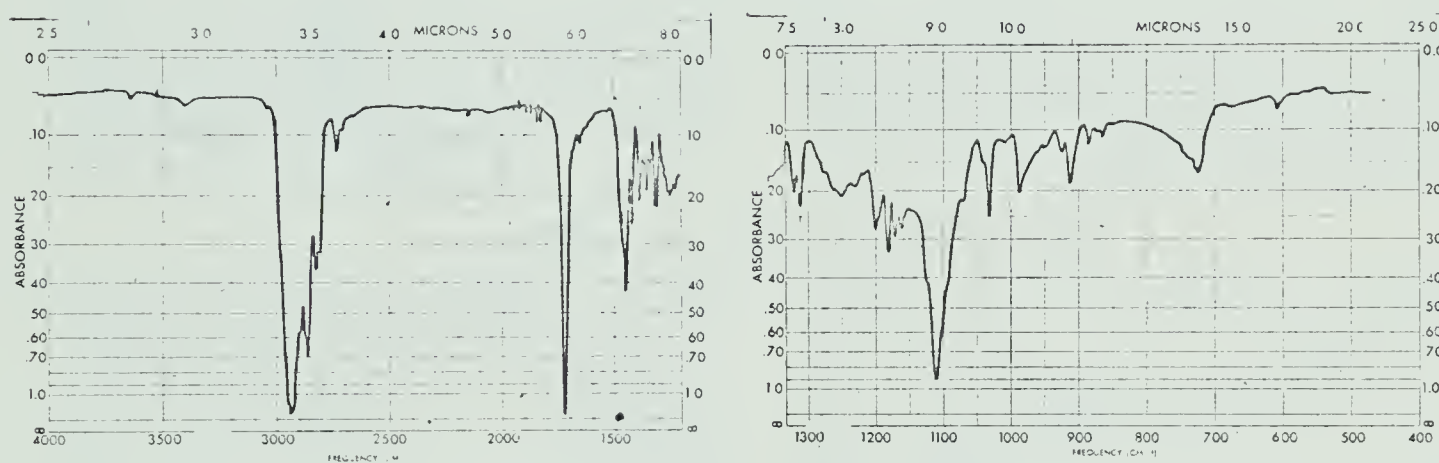


Fig. 34 The Methoxy Ketones 167 and 168

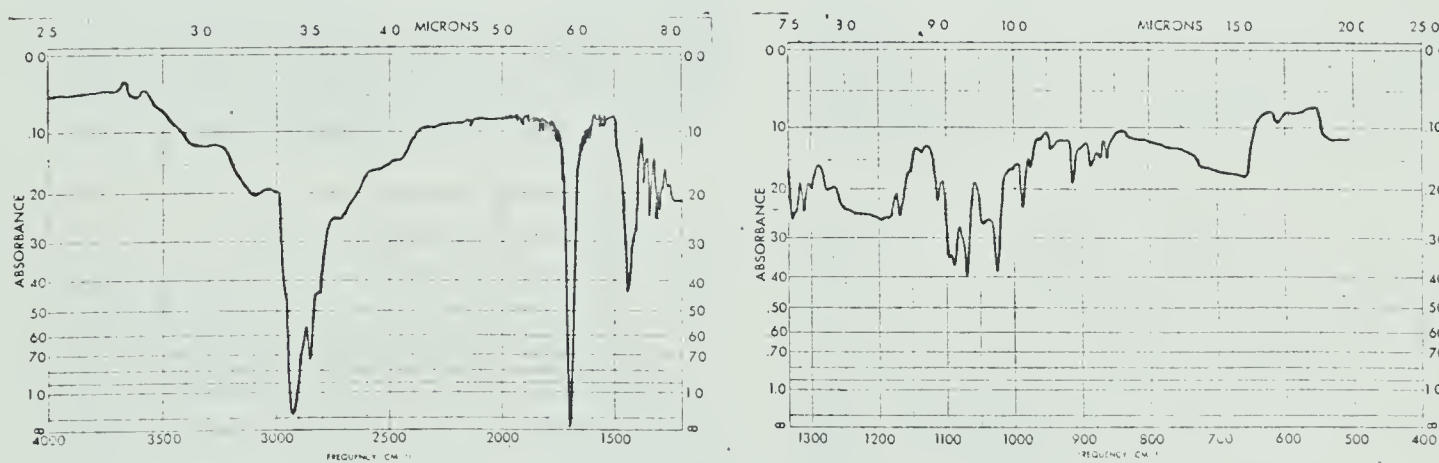


Fig. 35 The Alcohol 170



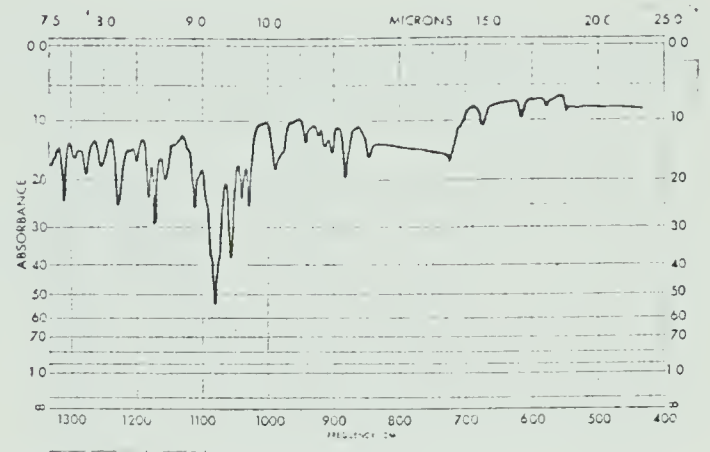
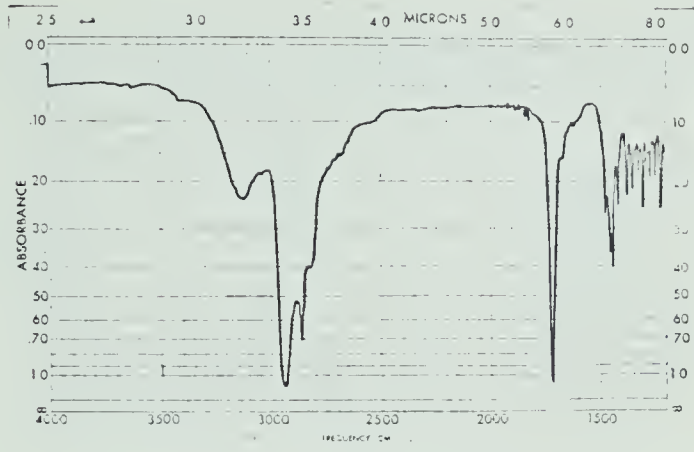


Fig. 36 The Alcohol 169

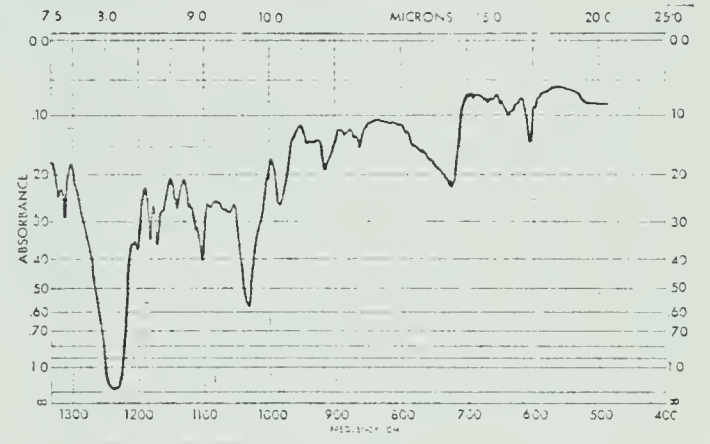
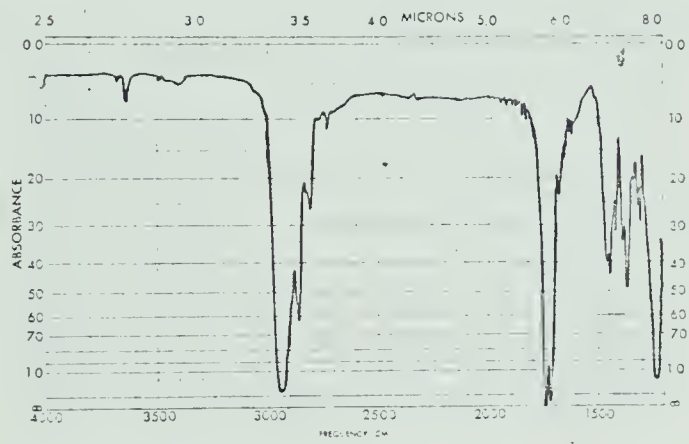


Fig. 37 The Acetate 171

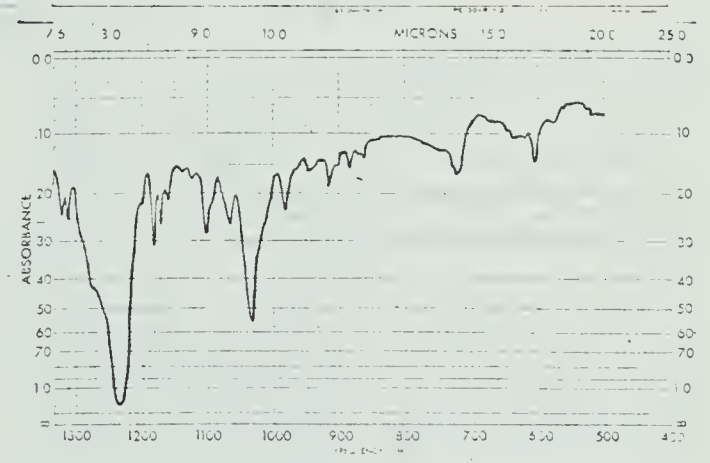
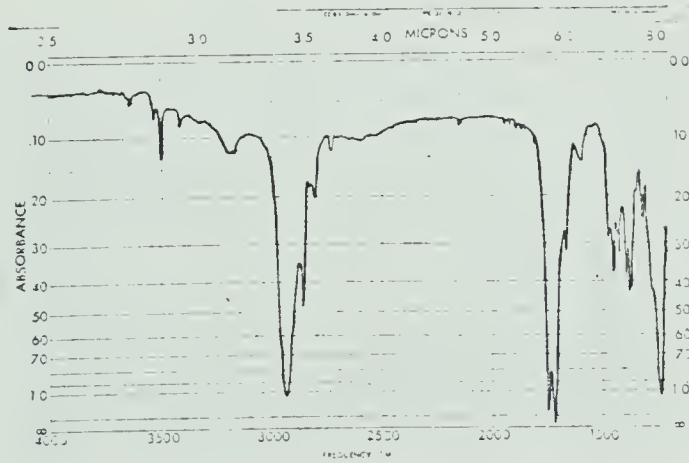


Fig. 38 The Acetate 172



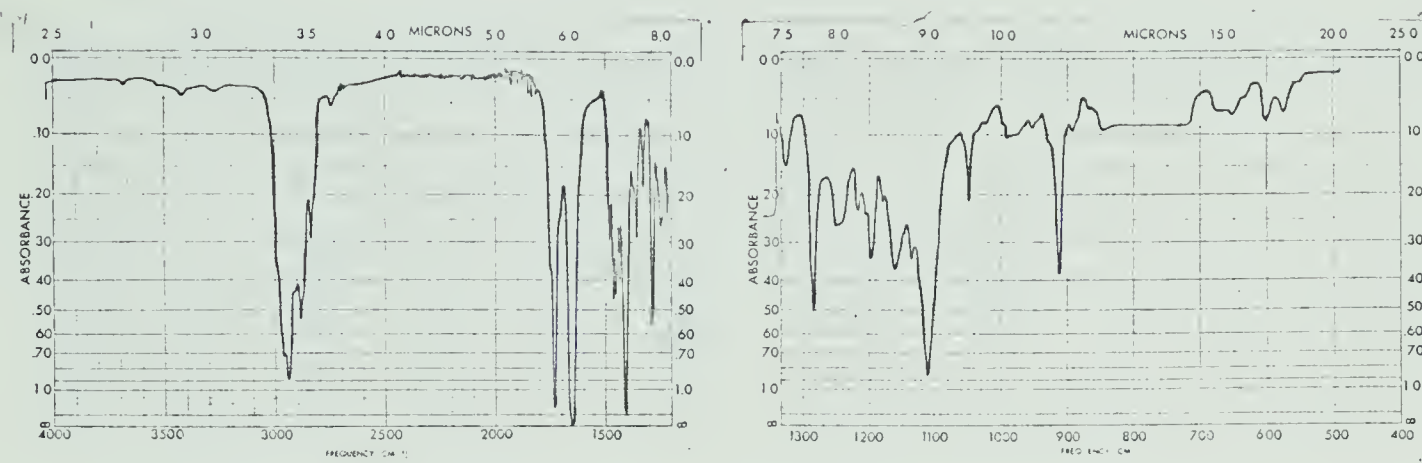


Fig. 39 The Methoxy Lactams 178 and 179

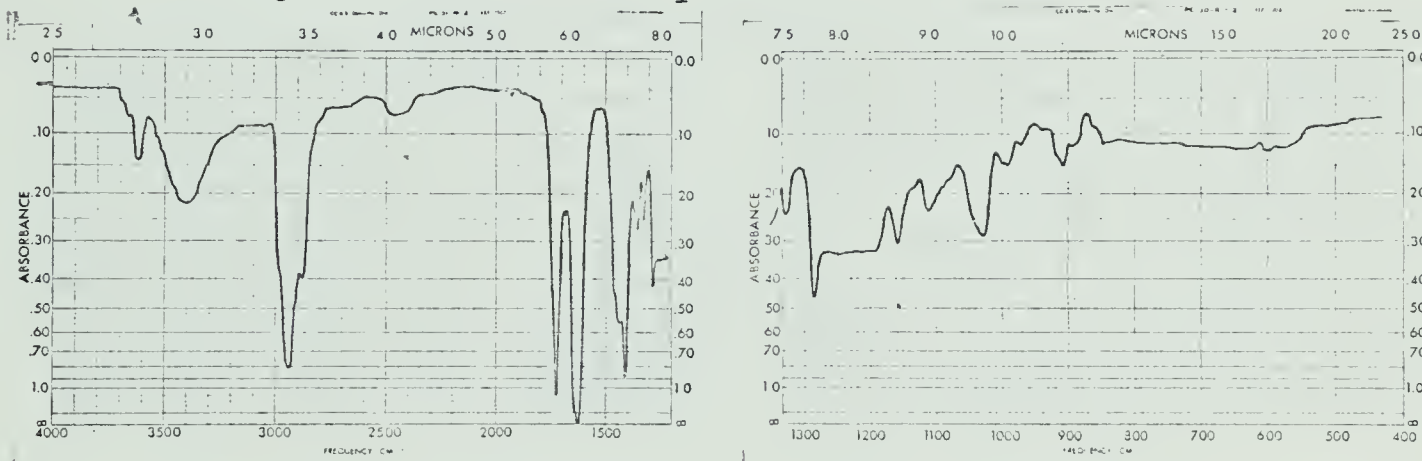


Fig. 40 The Lactam Alcohols 180 and 181

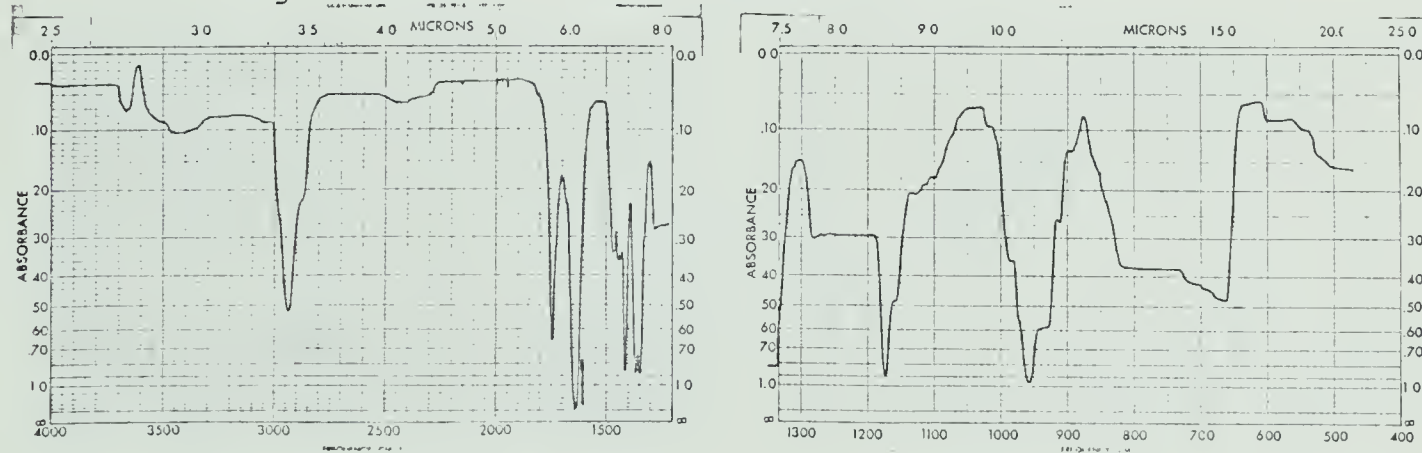


Fig. 41 The Mesyl Lactams 185 and 186



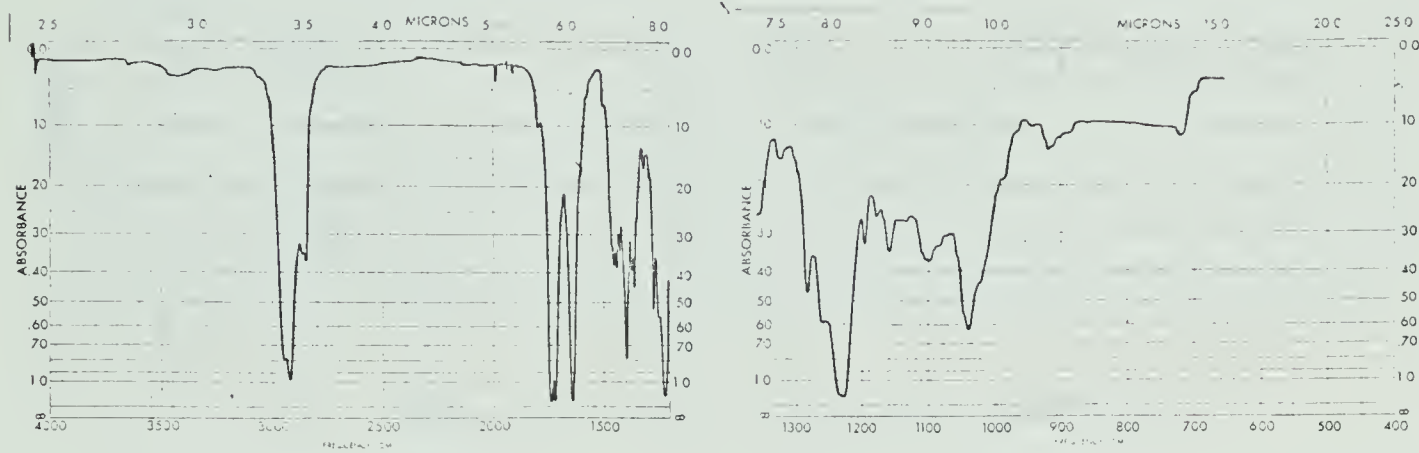


Fig. 42 The Lactam Acetate 188

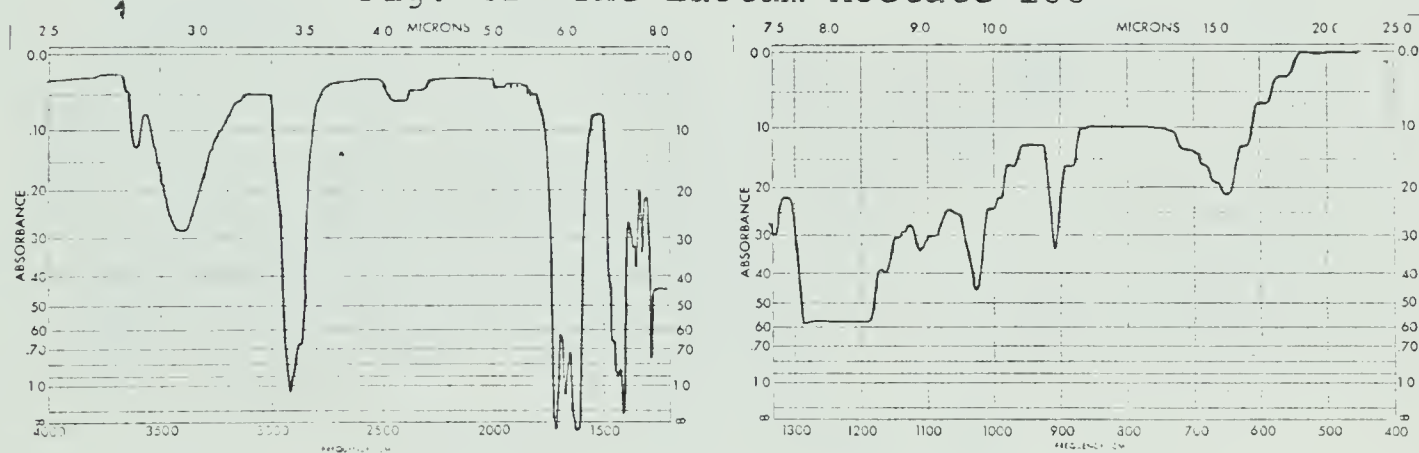


Fig. 43 The Lactam Alcohol 181

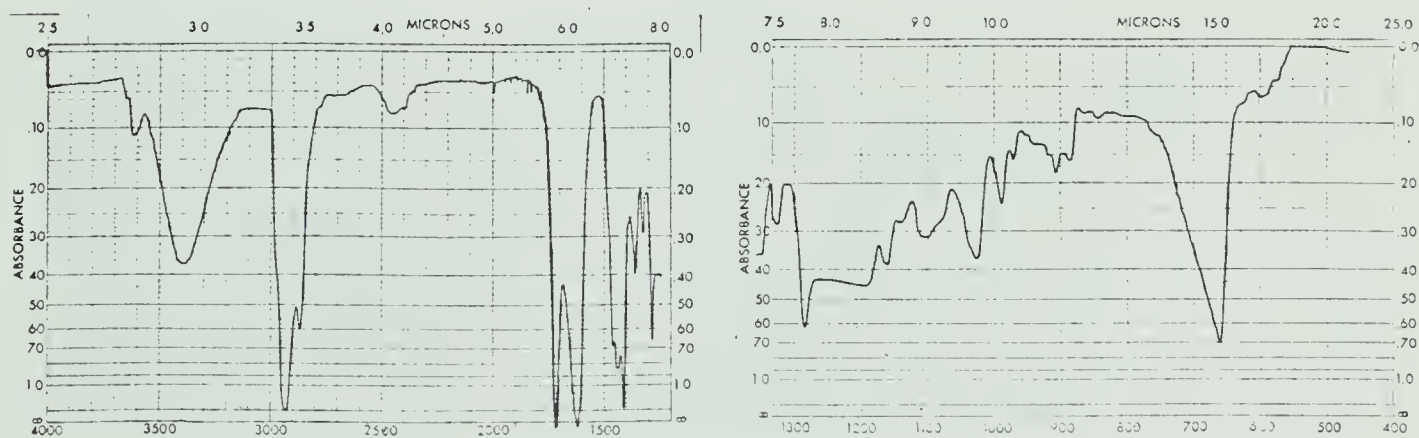


Fig. 44 The Lactam Alcohol 180







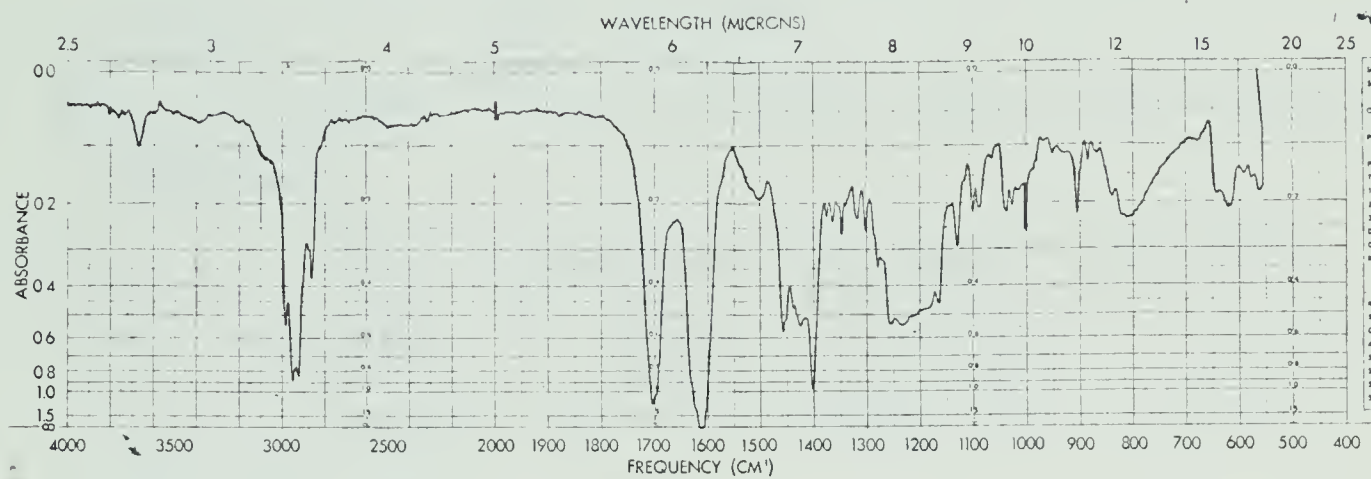


Fig. 45 The Lactams 177 and 184

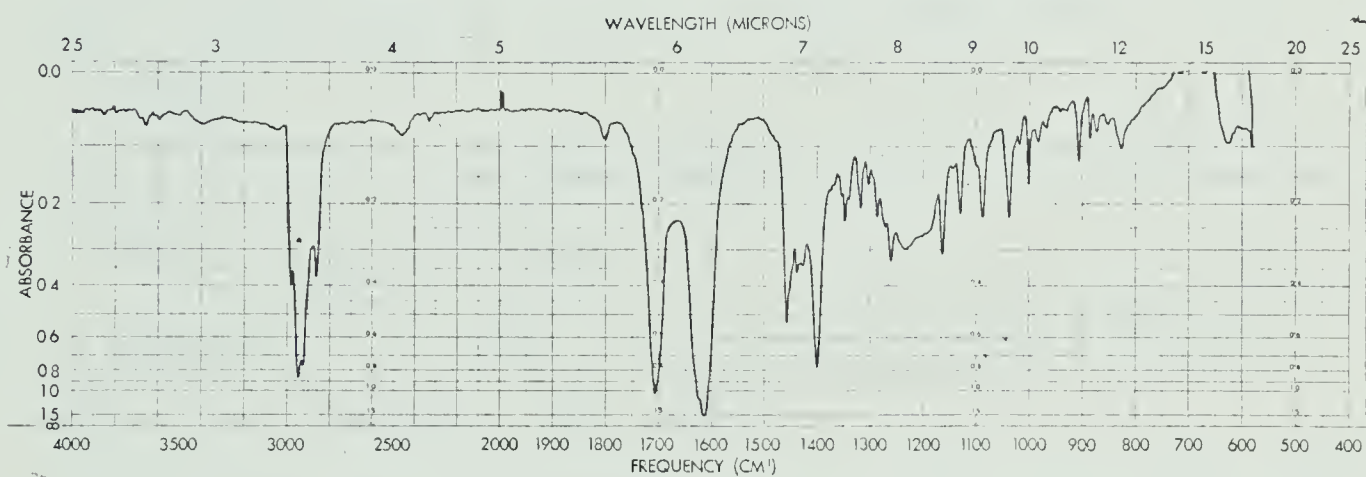


Fig. 46 The Lactam 184

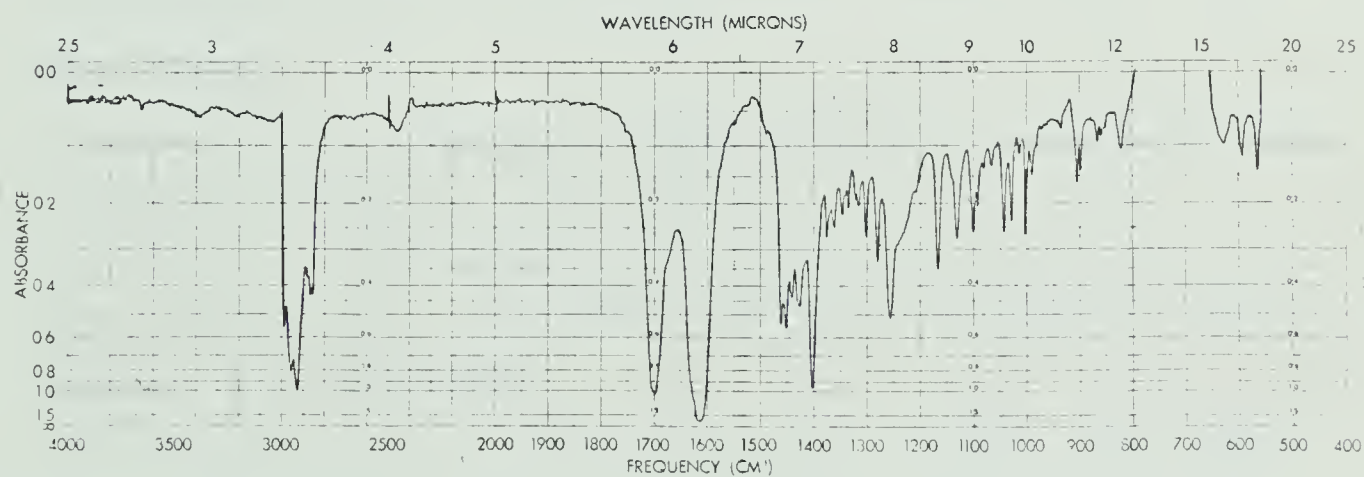


Fig. 47 The Lactam 177



BIBLIOGRAPHY

1. K. Bodeker, *Ann.*, 208, 363 (1881).
2. a) W. A. Harrison and D. B. Maclean, *Chem. Ind. (London)*, 261 (1960).  
b) F. A. L. Anet, *Tetrahedron Lett.*, No. 20, 13 (1960).  
c) W. A. Harrison, M. Curcumelli-Rodostamo, D. F. Carson, L. R. C. Barclay, and D. B. Maclean, *Can. J. Chem.*, 39, 2086 (1961).  
d) K. Wiesner and Z. Valenta, *Tetrahedron Lett.*, 187 (1961).  
e) W. A. Ayer, J. A. Berezowsky, and D. A. Law, *Can. J. Chem.*, 41, 649 (1963).
3. K. Wiesner, W. A. Ayer, L. R. Fowler, and Z. Valenta, *Chem. Ind. (London)*, 564 (1957).  
M. Przbylska and L. Marion, *Can. J. Chem.*, 35, 409 (1957).  
M. Przbylska and F. R. Ahmed, *Acta Crystallogr.*, 11, 718 (1958).
4. Z. Valenta, H. Yoshimura, E.E. Rogers, M. Ternbah, and K. Wiesner, *Tetrahedron Lett.*, No. 10, 26 (1960).
5. W. A. Ayer, J.A. Berezowsky, and G. G. Iverach, *Tetrahedron*, 18, 567 (1960).
6. W. A. Ayer and G. G. Iverach, *Can. J. Chem.*, 38, 1823 (1960).
7. D. B. Maclean and M. Curcumelli-Rodostamo, *Can. J. Chem.*, 44, 611 (1966).  
W. A. Szarek, K.A.H. Adams, M. Curcumelli-Rodostamo, and



- D. B. Maclean, Can. J. Chem., 42, 2584 (1964).
8. W. A. Ayer, J. K. Jenkins and N. Masaki, 1968, unpublished data.
  9. F. A. L. Anet, M.Z. Haq, N. H. Khan, W. A. Ayer, R. Hayatsu, S. Valverde-Lopez, P. Deslongchamps, W. Reiss, M. Ternbah, Z. Valenta, and K. Wiesner, Tetrahedron Lett., 751 (1964).
  10. W. A. Ayer, J. K. Jenkins, S. Valverde-Lopez, and R. H. Burnell, Can. J. Chem., 45, 433 (1967).
  11. W. A. Ayer, J. K. Jenkins, K. Piers, and S. Valverde-Lopez, Can. J. Chem., 45, 445 (1967).
  12. W. A. Ayer and K. Piers, Can. J. Chem., 45, 451 (1967).
  13. Y. Inubushi, H. Ishii, B. Yasui, M. Hashimoto, and T. Harayama, Tetrahedron Lett., 1537 (1966).
  14. B. Yasui, H. Ishii, T. Harayama, and Y. Inubushi, Tetrahedron Lett., 3967 (1966).
  15. H. Ishii, B. Yasui, T. Harayama, and Y. Inubushi, Tetrahedron Lett., 6215 (1966).
  16. Y. Inubushi, H. Ishii, T. Harayama, R. H. Burnell, W. A. Ayer, and B. Altenkirk, Tetrahedron Lett., 1069 (1967).
  17. Y. Inubushi, H. Ishii, and T. Harayama, Chem. Pharm. Bull. (Tokyo), 15, 250 (1967).
  18. H. Conroy, Tetrahedron Lett., No. 1, 34 (1960).
  19. K. Wiesner, Fortschr. Chem. Org. Naturstoffe (Springer-Verlag), 20 271 (1962).



20. F. A. L. Anet and M. V. Rao, *Tetrahedron Lett.*, No. 20, 9 (1960).
21. R. H. Burnell and D. R. Taylor, *Tetrahedron*, 15, 173 (1961).
22. R. H. Burnell and D. R. Taylor, *ibid.*, 18, 1467 (1962).
23. W. N. French and D. B. Maclean, *Can. J. Chem.*, 39, 2100 (1961).
24. W. A. Ayer and D. A. Law, *Can. J. Chem.*, 40, 2088 (1962).
25. W. A. Ayer, D. A. Law, and K. Piers, *Tetrahedron Lett.*, 2959 (1964).
26. Z. Valenta, P. Deslongchamps, R. A. Ellison, and K. Wiesner, *J. Amer. Chem. Soc.*, 86, 2533 (1964).
27. F. Bohlmann and O. Schmidt, *Chem. Ber.*, 97, 1354 (1964).
28. F. Bohlmann and R. Mayer-Mader, *Tetrahedron Lett.*, 171 (1965).
29. F. Bohlmann, D. Schumann, and O. Schmidt, *Chem. Ber.*, 99, 1652 (1966).
30. E. Colvin, J. Martin, W. Parker, and R. A. Raphael, *Chem. Commun.*, 596 (1966).
31. R. V. Stevens, Ph.D. Thesis, Indiana University (1966).
32. H. Dugas, R. A. Ellison, Z. Valenta, K. Wiesner, and C. M. Wong, *Tetrahedron Lett.*, 1279 (1965).
33. E. H. W. Böhme, Z. Valenta, and K. Wiesner, *Tetrahedron Lett.*, 2441 (1965).
34. K. Wiesner, I. Jirkovsky, M. Fisherman, and C. J. Williams *Tetrahedron Lett.*, 1523 (1967).





35. K. Wiesner and I. Jirkovsky, *Tetrahedron Lett.*, 2077 (1967).
36. K. Wisener and L. Poon, *Tetrahedron Lett.*, 4937 (1967).
37. H. Dugas, M. E. Hazenbourg, Z. Valenta, and K. Wiesner, *Tetrahedron Lett.*, 4931 (1967).
38. W. A. Ayer and G. G. Iverach, *Can. J. Chem.*, 42, 2514 (1964).
39. G. A. C. Cooke, Ph.D. Thesis, University of Alberta (1965).
40. R. H. Burnell, C. G. Chin, B. S. Mottoo, and D. R. Taylor, *Can. J. Chem.*, 41, 3091 (1963).
41. R. H. Burnell and D. R. Taylor, *Tetrahedron*, 18, 1467 (1962).
42. D. B. Maclean, *Can. J. Chem.*, 41, 2654 (1963).
43. W. A. Ayer, A. N. Hogg, and A. C. Soper, *Can. J. Chem.*, 42, 949 (1964).
44. W. Moffit, R. B. Woodward, A. Moscovitz, W. Klyne, and C. Djerassi, *J. Amer. Chem. Soc.*, 83, 4013 (1961).
45. W. N. Freanch and D. B. Maclean, *Can. J. Chem.*, 39, 2100 (1961).
46. F. Bohlmann, *Chem. Ber.*, 91, 2517 (1958).
47. F. A. L. Anet and C. R. Eves, *Can. J. Chem.*, 36, 902 (1958).
48. N. J. Leonard, *J. Amer. Chem. Soc.*, 78, 1984 (1956).



49. V. J. Traynelis and P. L. Pacini, J. Amer. Chem. Soc., 86, 4917 (1964).
50. J. Smuszkowicz, Advances in Organic Chemistry, 4, 1-114 (1963).
51. a) F. Zymalkowski and H. Rimek, Arch. Pharm. (Weinheim) 294, 759 (1961).  
b) F. Wille and L. Saffer, Ann., 568, 34 (1950).
52. a) R.B. Thompson, Org. Syn., Coll. 3, 278 (1955).  
b) R. Mozingo, Org. Syn., Coll. 3, 181 (1955).
53. J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds" Prentice-Hall Inc., Englewood Cliffs, N.J., 1965.
54. G. Stork, R. Terrell, and J. Smuszkowicz, J. Amer. Chem. Soc., 76, 2029 (1954).
55. L. A. Cohen and B. Witkop J. Amer. Chem. Soc., 77, 6595 (1955).
56. R. F. Parcell, J. Amer. Chem. Soc., 77, 6595 (1955).
57. a) N. P. Sen, Can. J. Chem., 40, 2189 (1962).  
b) C. S. Marvel and A. L. Tannebaum, Org. Syn., Coll. 1, 435 (1941)  
c) J. C. Cowan and C. S. Marvel, J. Amer. Chem. Soc., 58, 2277 (1936).
58. A. I. Scott, "Interpretation of Ultraviolet Spectra of Natural Products" The Macmillan Company, New York 1964.
59. R. Bonnett, V. M. Clark, A. Giddey, and A. Todd, J.



- Chem. Soc., 2087 (1959).
60. N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, J. Amer. Chem. Soc., 77, 439 (1955).
61. F. Bohlmann, W. Wiese, D. Rahtz, and C. Arndt, Chem. Ber., 90, 2176 (1958).
62. A. C. Soper, Private communication.
63. M. Friedlander, R. W. Mattoon, and Y. H. Ng, J. Org. Chem., 29, 3730 (1964).
64. A. Nickon and W. L. Mendelson, Can. J. Chem., 43, 1498 (1965).
- G. O. Schenk, Angew. Chem., 69, 579 (1957).
- A. Nickon and J. F. Bagli, J. Amer. Chem. Soc., 83, 1498 (1961).
- S. Masamune, J. Amer. Chem. Soc., 86, 290 (1964).
65. C. Djerassi, Chem. Rev., 43, 271 (1948).
66. C. O. Guss and R. Rosenthal, J. Amer. Chem. Soc., 77, 2549 (1955).
67. K. Piers, Ph.D. Thesis, University of Alberta (1966).  
"Technical Data on m-Chloroperbenzoic Acid", FMC.  
Corp.
68. G. Weifel and H. C. Brown, Org. React., 13, 1-54  
H. C. Brown, "Hydroboration", W. A. Benjamin Inc.,  
1962.
69. R. P. Holysz, J. Amer. Chem. Soc., 75, 4432 (1953).  
R. Joly, J. Warnant, G. Nomine, and D. Berlin, Bull.



- Soc. Chim. Fr., 366 (1958).
70. J. J. Beerebom, C. Djerassi, and D. Ginsburg, J. Amer. Soc., 70, 882 (1948).  
C. Djerassi, J. Amer. Chem. Soc., 71 1000, 1003 (1949).
71. J. Demaecker and R. H. Martin, Nature, 173, 266 (1966).
72. R. Engel, G. Just, and R. Buttery, Can. J. Chem., 39 1805 (1961).  
W. F. McGuekin and E. C. Kendall, J. Amer. Chem. Soc., 74, 5811 (1952).
73. G. F. H. Green and A. G. Long, J. Chem. Soc., 2532 (1961).  
T. H. Kritchevsky, D. L. Garnaise, and T. F. Gallagher, J. Amer. Chem. Soc., 74, 483 (1952).
74. A. Bowers, E. Deniot, L. Cuellar-Ibanez, Ma. Elena Cabezas, and H. J. Ringold, J. Org. Chem., 27, 1862 (1962).
75. E. E. Glover and G. Jones, J. Chem. Soc., 3021 (1958).
76. R. C. Elderfield, B. M. Pitt, and I. Wempen, J. Amer. Chem. Soc., 72, 1334 (1950).
77. C. R. Narayanan and K. N. Iyer, J. Org. Chem., 30, 1734 (1965).
78. R. D. Youssefyeh and Y. Mazur, Chem. Ind. (London) 609 (1963).
79. T. P. Povlock, Tetrahedron Lett., 4131 (1967).
80. C. F. Huebner and E. Wenkert, J. Amer. Chem. Soc., 77,





4180 (1955).

E. E. Van Tamelin and P. D. Hance, *ibid*, 77, 4692  
(1955).

81. F. Bohlmann and D. Schumann, *Tetrahedron Lett.*, 243  
(1965).

82. G. Stork, Private Communication to W. A. Ayer.









**B29886**